Bis-enolates with extended π-conjugation are powerful nucleophiles. Study of their alkylation reactions with very hindered C-electrophiles

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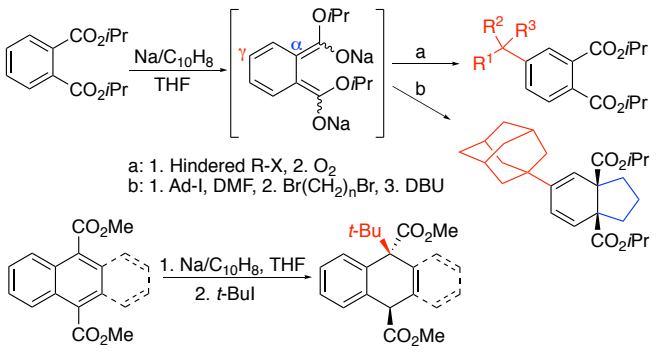


Abstract: *Bis*-enolates with extended π-conjugation, prepared by alkali metal mediated reduction of several aromatic and unsaturated diesters, can be efficiently and regioselectively alkylated with very hindered C-electrophiles, such as neopentyl, secondary and tertiary alkyl

halides and tosylates. A one-step synthesis of 4-alkyl phthalates was derived from the reductive-alkylation of a phthalate diester with hindered halides followed by rearomatization with oxygen. Additionally, synthetic protocols have been developed to efficiently prepare complex fused- or spiro-bicycles from diisopropyl phthalate in just one or two steps.

Introduction

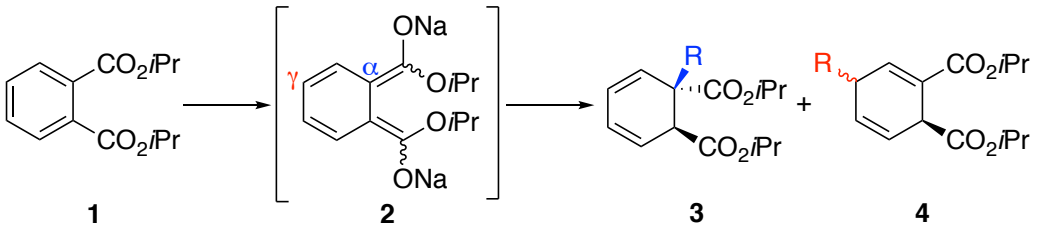
Reductive alkylation reactions are useful tools to build complex structures from simple aromatic compounds.[1] In this particular topic we have been studying the reductive alkylation of aromatic diesters, e.g. dialkyl phthalates, promoted by alkali metals under ammonia free conditions[2] or mediated by tin-lithium reagents through a nucleophilic stanna-Brook rearrangement,[3] to gain access to complex polycyclic systems. We have proposed that the key intermediates of these reactions are relatively stable *bis*-enolates with extended π-conjugation that can be trapped with primary α,ω-*bis*-electrophiles to give fused bicyclic compounds.[2] These alkylations occur regioselectively, with the C-C bond formation taking place at both the α positions of the enolate moieties, resulting in two adjacent quaternary centers being formed in the process. Reductive alkylation with different primary *bis*-electrophiles was achieved starting from anthracene[4] and naphthalene[5] diesters as well, to give a variety of fused and bridged polycycles. Although two possible nucleophilic sites are available in these dianionic species, α- or γ- to each enolate group, exclusive α-alkylation was always observed when primary halides or tosylates were used as electrophiles (Scheme 1).

There are countless examples in the literature of C-C bond-forming reactions between a carbon dianion and primary electrophiles.[6] In stark contrast, reports of alkylations of carbon dianions with more hindered (secondary) alkyl halides are scarce and there are no reports of alkylations with tertiary or neopentylic electrophiles, probably due to the fact that

elimination or rearrangement processes become the predominant reaction pathways for these highly basic nucleophiles when the C-electrophiles used are somewhat hindered.[7] We now report the unexpected finding that *bis*-enolates with extended π-conjugation, such as **2**, undergo efficient, regioselective alkylation reactions with very hindered electrophiles such as secondary, neopentylic, and even tertiary alkyl halides. As a direct application of this transformation, from its simplest case, namely the alkylation of phthalate diester **1**, a regioselective one-step synthesis of 4-alkyl phthalates has been developed.

As relevant precedents of our work we should mention that the synthesis of alkyl-substituted arenes via reductive alkylation-rearomatization of aromatic carboxylic acids has been reported. The procedure employed involves performing a Birch reaction[8] on benzoic acids followed by an alkylation of the intermediate enolate formed and then carrying out a decarbonylative rearomatization on the resulting cyclohexadiene carboxylic acid.[9] In the same vein, different dearomatization/rearomatization approaches have also been successfully developed for the regioselective introduction of up to three alkyl groups onto an aromatic ring.[10, 11, 12] However only primary alkyl halides or the relatively unhindered *i*PrBr have been used successfully as electrophiles in all the aforementioned synthetic sequences. Thus, the attachment of hindered (bulky) alkyl groups to aromatic rings *via* the alkylation of anionic species remains a challenge which has remained unaddressed to date.

Scheme 1. Dearomatization/Alkylation of Phthalate 1

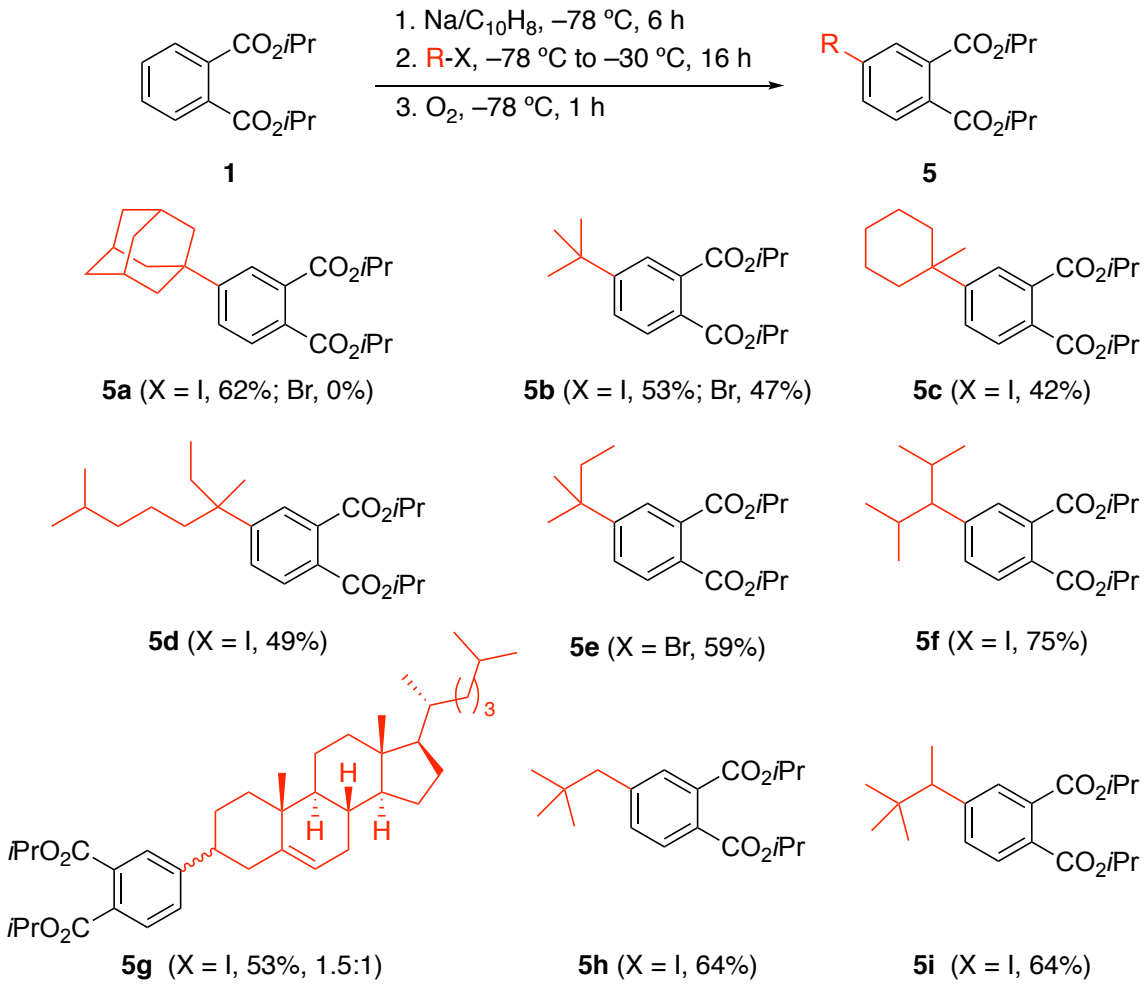


Results and Discussion

We have previously shown that the generation of *bis*-enolates, such as **2** (Scheme 1, more on the characterization of the nature of this dianionic intermediate below), from

aromatic diesters can be easily accomplished by reaction of phthalates with alkali metals in the presence of naphthalene as an electron carrier in THF as solvent.[13] To test the feasibility of alkylating dianion **2** with hindered halides we initially chose 1-iodoadamantane as the electrophile.[14] In a typical reaction, diisopropyl phthalate (**1**) was treated with excess sodium naphthalene in THF for 6 h at –78 ºC, 1-iodoadamantane in DMF was then added and the reaction mixture was stirred for 16 h while letting it warm up to –30 ºC. Examination of the crude reaction product showed that adamantylation had indeed taken place to give the γ-alkyl-cyclohexadienes **4** (R = 1-adamantyl, as a mixture of diastereoisomers), along with an alkylated and rearomatized product **5** (see Scheme 2). Cyclohexadienes **4** (a mixture of *cis* and *trans* isomers) showed a remarkable tendency to rearomatize under attempted chromatographic purification, or simply upon standing, so we decided to directly oxidize the crude reaction mixture before performing the aqueous work-up, to obtain directly the adamantyl-substituted phthalate **5a** (see Scheme 2). For this purpose we tested DDQ, air and oxygen as oxidants, and found that the latter provided a higher yield of a cleaner rearomatized product. Thus, the optimized alkylation-rearomatization procedure involved the treatment of the sodium *bis*-enolate derived from phthalate **1** with 1-iodoadamantane for 16 h at –30 ºC, followed by bubbling oxygen through the reaction mixture for 1 hour. The desired product **5a** was isolated in 62% yield and its structure was confirmed by X-ray crystallography. Attempted reductive alkylation with lithium/naphthalene at -30 ºC followed by treatment with 1-iodoadamantane was unsuccessful and only led to reduced (non-alkylated) products.

Scheme 2. γ-Alkylation with Hindered Halides followed by Rearomatization



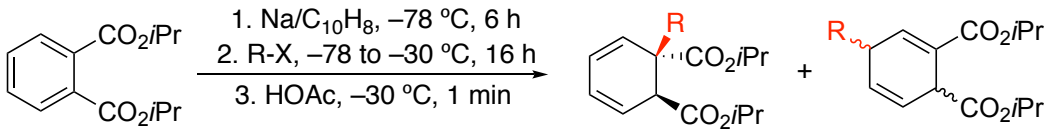
When *t*-butyl iodide was used as electrophile, the *t*-butylated phthalate **5b** was isolated in 53% yield. In this case, reductive/alkylation with lithium/naphthalene and *t*-butyl iodide was also effective to give **5b** in a slightly lower yield (46%). Analogous results were obtained with the *t*-alkyl halides methylcyclohexyl iodide and 6-iodo-2,6-dimethyloctane, which gave diesters **5c** (42% yield) and **5d** (49% yield), respectively (see Scheme 2).

Tertiary alkyl bromides were also successfully used as electrophiles in this transformation and alkylation of **2** with *t*-butyl bromide gave 5-*t*-butylphthalate **5b**, although in a slightly lower yield (47%) than the reaction with the corresponding iodide. In the same vein, the use of *t*-pentyl bromide as electrophile afforded **5e** in 59% yield. In contrast, the C-C bond forming reactivity decreased dramatically when 1-bromoadamantane was reacted with *bis*-enolate **2**, as no alkylated product was observed in the crude reaction mixture.

The behavior of other types of very sterically hindered electrophiles was next examined. Efficient, exclusive γ-alkylation was also observed upon reaction of *bis*-enolate **2** with 3-iodo-2,4-dimethylpentane, a very hindered secondary electrophile, which gave a 75% yield of the desired alkylated product **5f**. A chiral hindered secondary substrate, 3-β-iodo-cholest-5-ene, also led to the expected γ-alkylated product **5g** in 53% yield, but as a 1.5:1 mixture of epimers at C3 (more on the lack of stereospecificity in this reaction later). In the same vein, we decided to study the behavior of *bis*-enolate **2** towards neopentyl halides, notorious very poor electrophiles.[14b,15] In our case, efficient alkylation of **2**, without rearrangement of the neopentyl moiety, was achieved with neopentyl iodide (to give **5h** in 64% yield) and with 3-iodo-2,2-dimethylbutane (to give **5i** in 64% yield).

The fact that *bis*-enolate **2** is exclusively alkylated at the γ position with very hindered electrophiles, while it reacts with complete regioselectivity through the α position with primary electrophiles[2,3a] prompted us to examine in more detail the alkylation of our workhorse dianionic nucleophile with electrophiles of varying steric demands (Table 1). We initially examined its reaction with isopropyl iodide and we observed that the alkylation took place solely at the *bis*-enolate α-carbon. By quenching this reaction with HOAc at –30 ºC, the unconjugated diene **3a** was obtained as the main product (72% isolated yield). The effect of the leaving group was next examined and we found that isopropyl bromide also performs well in the alkylation reaction, the desired **3a** being isolated in 80% yield. Unsurprisingly, no alkylation was observed when the much poorer electrophile isopropyl chloride was used (Table 1).

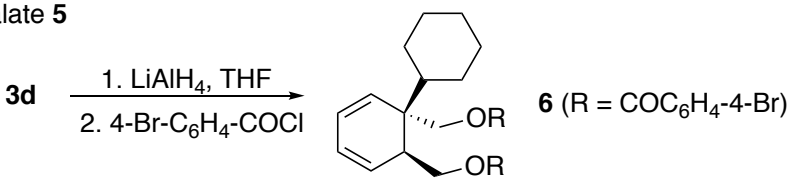
Table 1. Alkylations of 1 with Secondary Halides. Effect of the Leaving Group



1 **3** **4**

entry	R	X	α-alkylation	γ-alkylation[a]
1	*i*Pr	I	**3a**, 72%	-
2	*i*Pr	Br	**3a**, 80%	-
3	*i*Pr	Cl	**3a**, 0%	-
4	Cyclobutyl	Br	**3b**, 86%	-
5	Cyclopentyl	I	**3c**, 67%	-
6	Cyclopentyl	Br	**3c**, 84%	-
7	Cyclohexyl	I	**3d**, 74%	**4d**, 7%
8	Cyclohexyl	Br	**3d**, 79%	tr
9	Cyclohexyl	OTs	**3d**, 22%	-
10	Cycloheptyl	I	**3e**, 51%	**4e**, 21%
11	Cycloheptyl	Br	**3e**, 83%	tr
12	Cycloheptyl	OTs	**3e**, 56%	-
13	Cyclooctyl	I	**3f**, 34%	**4f**, 21%
14	Cyclooctyl	Br	**3f**, 80%	**4f**, 3%
15	Cyclooctyl	OTs	**3f**, 47%	-
16	4-Tetrahydropyranyl	Br	**3g**, 43%	-
17	*N*-Boc-4-piperidinyl	Br	**3h**, 76%	-

[a] The product of γ-alkylation **4** was isolated as the corresponding rearomatized phthalate **5**

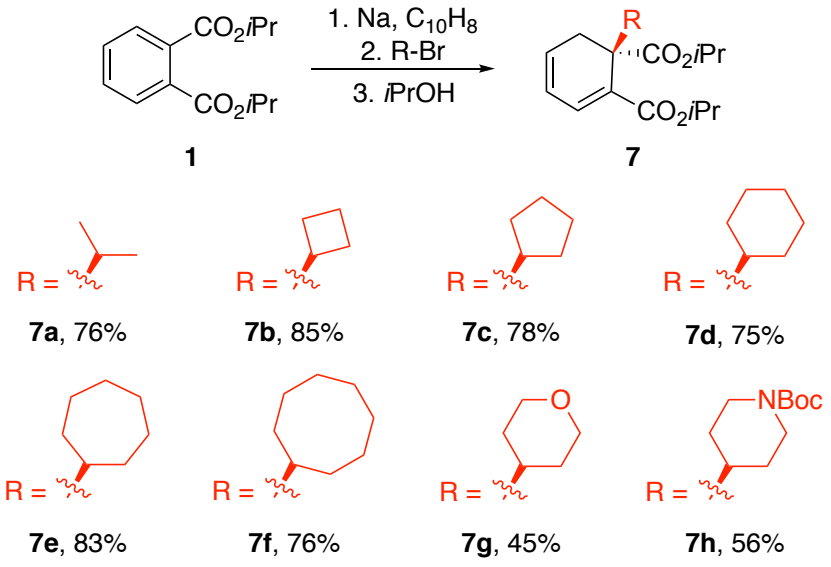


We then surveyed the behavior of the family of 4- to 8-membered cycloalkyl halides as electrophiles, so the effects of ring size and leaving group could be evaluated. As shown in Table 1, the best results (in terms of regioselectivity) were obtained when bromide was used as the leaving group, the corresponding α-alkylated products **3** being isolated in good yields (**3b**: 86%, **3c**: 84%, **3d**: 79%, **3e**: 83%, **3f**: 80%, respectively). Cycloalkyl tosylates reacted more sluggishly and the desired α-alkylated products were obtained only in low to moderate yields (**3d**: 22%, **3e**: 56%, **3f**: 47%). In contrast, alkylation of *bis*-enolate **2** with cycloalkyl iodides led to mixtures of regioisomers **3** and **4**. The regioselectivity of the alkylation decreased in the series cyclohexane (10:1) > cycloheptane (~5:2) > cyclooctane (~3:2). As

examples of the use of heteroatom containing electrophiles, we treated *bis*-enolate **2** with 4-bromotetrahydropyran and with 1-Boc-4-bromopiperidine to obtain the α-alkylated products **3g** and **3h** in 43% and 76% yield, respectively, thus indicating that the reaction conditions tolerate the presence of heteroatoms and a Boc-protecting group in the electrophile. NOE experiments to establish the stereochemistry of **3** were inconclusive, but the relative *trans* configuration of the ester groups of **3** was unambiguously determined by X–ray crystallography of a crystalline derivative of **3d**, obtained by $LiAlH_4$ reduction to the corresponding diol and subsequent derivatization with *p*-bromobenzoyl chloride to the diester **6**.

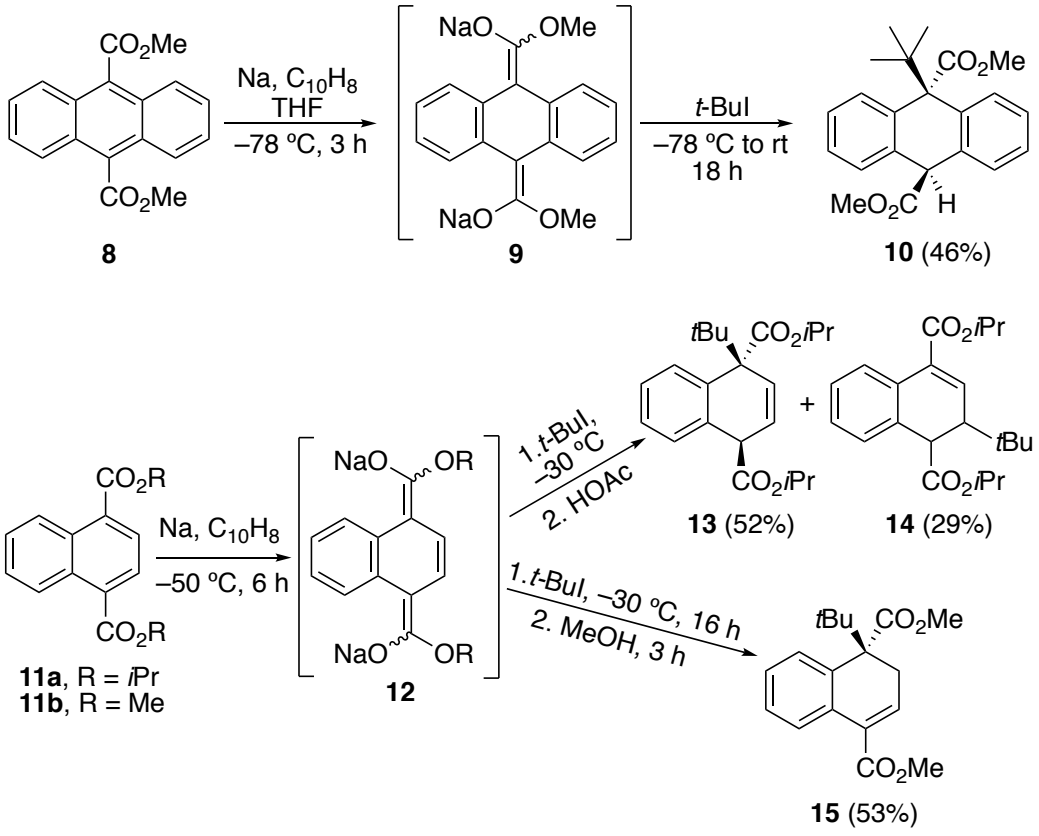
Cyclohexadienes **3** tend to slowly equilibrate to the conjugated isomer **7** on standing (Scheme 3). We took advantage of this behavior by quenching the reaction mixture with *i*PrOH instead of HOAc, and subsequent stirring of the reaction mixture for 3 h at rt so as to equilibrate isomers **3** towards the more stable, fully conjugated regioisomer **7**. Under these conditions, compounds **7** were prepared in yields comparable to those obtained for their kinetic regioisomers **3** (see Scheme 3).

Scheme 3. Reductive-Alkylation with Secondary Bromides



The ease of the alkylation of *bis*-enolate **2** with very hindered electrophiles, including tertiary and neopentyl halides, is exceptional and prompts questions about what could be the origin of the high nucleophilicity of this species. We speculated that the dianionic nature of *bis*-enolate **2** could contribute to its nucleophilic strength, due to the high negative charge of this type of intermediate. However, the most thoroughly studied *bis*-enolate in the literature, the dianion derived from methyl acetoacetate, has been efficiently alkylated only with primary alkyl halides and with isopropyl iodide. The only published attempt at alkylating this dianion with a tertiary electrophile, namely *t*-butyl bromide, was unsuccessful.[16] In our hands, and following the reaction conditions described by Weiler et al., treatment of the dianion of methyl acetoacetate with *t*-butyl iodide or with 1-adamantyl iodide failed to produce any alkylated products.

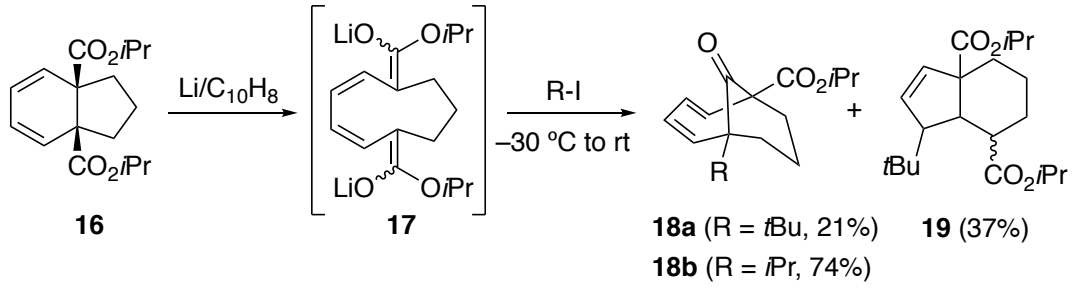
Scheme 4. Scope of Reductive Alkylation of Aromatic Diesters with *t*-Butyl Iodide



To study if the extended π-conjugation of our nucleophile plays a role in the observed reactivity towards very hindered electrophiles, we surveyed the alkylation reactions of several types of analogously π-conjugated *bis*-enolates obtained from anthracenic and naphthalenic diesters (Scheme 4). Reduction of dimethyl anthracene-9,10-dicarboxylate (**8**) with sodium/naphthalene gives a *bis*-enolate with extended cross-conjugation (**9**) that can only undergo alkylation at its 9/10 positions, so its reaction with a tertiary halide would form two contiguous quaternary centers in a very crowded environment. Despite this perceived difficulty, anthracene **8** could be successfully reductively alkylated using *t*-butyl iodide as electrophile, and the desired *t*-butyl dihydroanthracene **10** was isolated in 46% yield.[17] The relative *trans* configuration of the ester groups was unambiguously established by single-crystal X-ray diffraction analysis of diester **10**. The results were more satisfactory when we reacted *t*-butyl iodide with a slightly less sterically demanding, related cross-conjugated nucleophile, the *bis*-enolate **12** obtained from naphthalene-1,4-dicarboxylate (**11a**) under our typical reductive alkylation conditions. Analysis of the crude reaction mixture from this reaction revealed that the desired *t*-butylation had taken place, albeit in a non-regioselective manner: a 2:1 mixture of α- and γ- *t*-butylated products was obtained (Scheme 4). Surprisingly, the more crowded α-alkylated product **13**, possessing two contiguous quaternary centers, was isolated as the main product in 52% yield, while the less sterically encumbered γ-alkylated product **14** was isolated in 29% yield as a mixture of *cis-trans* isomers. The relative stereochemistry of **13** was tentatively assigned by analogy with anthracene **10**. In an attempt to direct the alkylation of **12** towards the α-position by reducing the steric demands posed by the ester group, we examined the behavior of the methyl diester analogue **11b**. Under the typical reaction conditions, reductive alkylation of **11b** occurred regioselectively to afford only the α-alkylated diester **15** in 53% yield.[18]

Encouraged by the observation that this exceptionally high nucleophilic behavior is not restricted to monocyclic *bis*-enolate **2** but that it is also displayed by other *bis*-enolates with extended conjugation, we decided to explore the C-C bond forming reactivity of an analogous conjugated dianion not directly derived from the reduction of an aromatic diester. For this purpose we studied the alkylation reactions of *bis*-enolate **17** (Scheme 5), an intermediate formed in the lithium/naphthalene mediated ring-opening reaction of 6,5-fused bicycle **16**.[2] *Bis*-enolate **17** has been previously stereoselectively protonated to give 9-membered carbocycles and also mono- and di-alkylated with methyl iodide.[2] For the purpose of this study, we treated *bis*-enolate **17** with *t*-butyl iodide and obtained a mixture of alkylated bicyclic compounds **18a** and **19** (Scheme 4). Both products incorporate one *t*-butyl group in their structures. Bicyclo[4.3.1]decanone **18a** (isolated in 21% yield) derives from alkylation of one of the enolate groups of **17** at its α-position to give a monoenolate that further evolves via a Dieckmann condensation. Alternatively, alkylation at the γ-position of one of the enolates of **17** leads to a monoenolate that evolves through a conjugate addition to the newly formed α,β-unsaturated ester to give hidrindane **19** (isolated in 37% yield). When a secondary halide was used to quench *bis*-enolate **17**, alkylation took place exclusively at the α-position and the product of the Dieckmann condensation **18b** was isolated in 74% yield (Scheme 5).

Scheme 5. Alkylation of *bis*-Enolate 17



16 **17** **18a** (R = *t*Bu, 21%) **19** (37%)
18b (R = *i*Pr, 74%)

We speculate that the extended π-conjugation of our *bis*-enolates has two positive effects on the nucleophilic prowess of this type of dianions: (1) it moderates the high basicity expected for such dianionic species, thus decreasing their tendency to give competitive elimination reactions with encumbered electrophiles, and (2) it raises the energy level of their HOMO, thus increasing both their nucleophilicity (in alkylations *via* an S_N2 mechanism) and their potential to act as one-electron donors (a key step in alkylations *via* an $S_{RN}1$ mechanism).[19] Furthermore, the planar (or quasi-planar) nature of these intermediates will likely result in reduced non-bonding (repulsive) interactions in the transition state of the C-C bond forming step, positively contributing to the success of the alkylation processes (irrespective of the particular mechanism followed).

We then tried to put on a firmer ground the nature of the reactive nucleophile and also to better delineate the alkylation mechanism. To evaluate if the reactive intermediate is dianionic in nature (as opposed to, for instance, an anion radical) we treated phthalate **1** with $Na/C_{10}H_8$ and monitored the progress of the formation of our nucleophilic species by ^1H NMR and by EPR. When we followed by ^1H NMR the evolution of a mixture of Na (1000 mol%) and naphthalene (110 mol%) treated with phthalate **1** (100 mol%) in THF-d_8, we observed the complete disappearance of the starting material and the appearance of a new product with four sharp signals, at δ 6.46 (H5), 4.98 (H6), 4.50 (H2), and 1.17 ppm (H1), consistent with the structure of a symmetrical disodium *bis*-enolate.[20] The ^1H-NMR spectrum of the species obtained with Na/naphthalene is practically identical to that of the dilithium *bis*-enolate obtained by treating phthalate **1** (100 mol%) with Me_3SnLi (prepared by mixing MeLi (250 mol%) and Me_6Sn_2 (250 mol%) in THF-d_8 at -78 ºC) [3a] in THF-d_8 that we had completely and unambiguously characterized in a previous investigation.[3a] The sharpness of the proton signals and the close similarity between the spectra of the Na and Li species strongly points to a dianionic nature for the nucleophile obtained under our reductive

conditions (Figure S2, Supporting Info). To discard the possibility that a radical anion is being formed under these conditions, we determined the EPR spectrum of our nucleophile **2**. A mixture of sodium/naphthalene and phthalate **1** in THF showed the signals for only one radical species. The observed signal was identical to that of the sodium/naphthalene radical when the EPR spectra of both samples were acquired under the same conditions (Figure S3, Supporting Info). These spectroscopic experiments point to the conclusion that *bis*-enolate **2** is the predominant species and the reactive nucleophile formed when phthalate **1** is reacted with $Na/C_{10}H_8$.

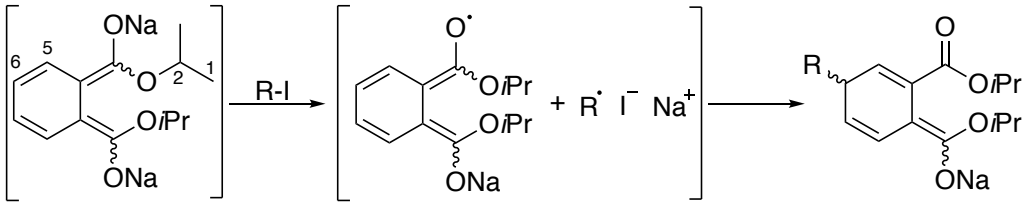
With regards to the alkylation mechanism, we deemed that *bis*-enolate **2** could be alkylated via S_N2 and/or $S_{RN}1$ mechanisms. In the absence of steric hindrance, the S_N2 mechanism should be energetically favored over the $S_{RN}1$ (a mechanism which involves an electron transfer, ET). In contrast, the ET pathway ($S_{RN}1$) could be more favorable for the alkylation of **2** with more hindered electrophiles.[21]

We established a rough order of reactivity for the alkylation of *bis*-enolate **2** with several representative C-electrophiles (adamantyl, *t*-butyl, cyclopentyl and neopentyl iodides were used) by quenching the reactions after a short period (15 minutes) and establishing the conversion to the alkylated product by ^{1}H-NMR analyses of the crude reaction mixtures. Surprisingly the highest conversions (faster alkylations) were obtained for the reactions of **2** with the tertiary electrophiles *t*-butyl iodide (>95%) and adamantyl iodide (>85%), followed by those of cyclopentyl iodide (78%) and then by that of neopentyl iodide (50%). We rule out the possibility of an S_N1-type mechanism[22] for the alkylation of the tertiary electrophiles due to the fact that they react very rapidly with *bis*-enolate **2** at very low temperatures and in a non-polar solvent, such as THF, which are quite incompatible conditions for this type of mechanism to operate at such high rates, especially for the adamantyl system. The fact that tertiary electrophiles give faster alkylation reactions than secondary and primary ones (in

this order) strongly argues for the occurrence of an $S_{RN}1$ mechanism in which an electron transfer from an appropriate electron source induces the cleavage of the alkyl-halide bond, generating a radical which is then alkylated by an anionic species. The fact that *t*-butyl iodide reacts faster than adamantyl iodide simply follows the relative ease of formation of their respective radicals (a planar *t*-butyl and a non-planar 1-adamantyl radical).

If the reaction indeed occurs via an $S_{RN}1$ mechanism, a transfer of an electron from the nucleophile (*bis*-enolate) or from another suitable electron source (sodium or sodium naphthalene) to the electrophile has to take place in the initiation step. To clarify which is the possible electron source, we run two alkylation experiments with *bis*-enolates generated under different conditions: (1) the disodium *bis*-enolate was generated with sodium at -30 ºC, in the absence of naphthalene, and (2) the dilithium *bis*-enolate was generated with Me_3SnLi, under stanna-Brook, ionic conditions.[3a] In both cases we observed the adamantylated product, although under stanna-Brook conditions it was necessary to warm the dilithium *bis*-enolate reaction mixture to 0 ºC to obtain a good conversion to the alkylated product. As the alkylation takes place in all the tested conditions, i.e. in the absence of sodium or sodium naphthalene as well, we proposed that the *bis*-enolate is the electron source that transfers one electron to the alkyl halide (Scheme 6). The reaction between a *bis*-enolate and hindered alkyl halides then involves a dissociative electron transfer where the electron transfer to the alkyl halide and the cleavage of the carbon-halogen bond are concerted to give the alkyl radical and iodide (I^-).[23, 24] Finally, coupling of the radical anion **20** with the alkyl radical affords the monoenolate **21** (Scheme 6). The monoenolate **21** was shown to be stable in the presence of excess electrophile. These results taken altogether indicate that the alkylation of π-extended *bis*-enolates with hindered substrates occurs by an $S_{RN}1$-like mechanism.

Scheme 6. Proposed $S_{RN}1$-type Mechanism



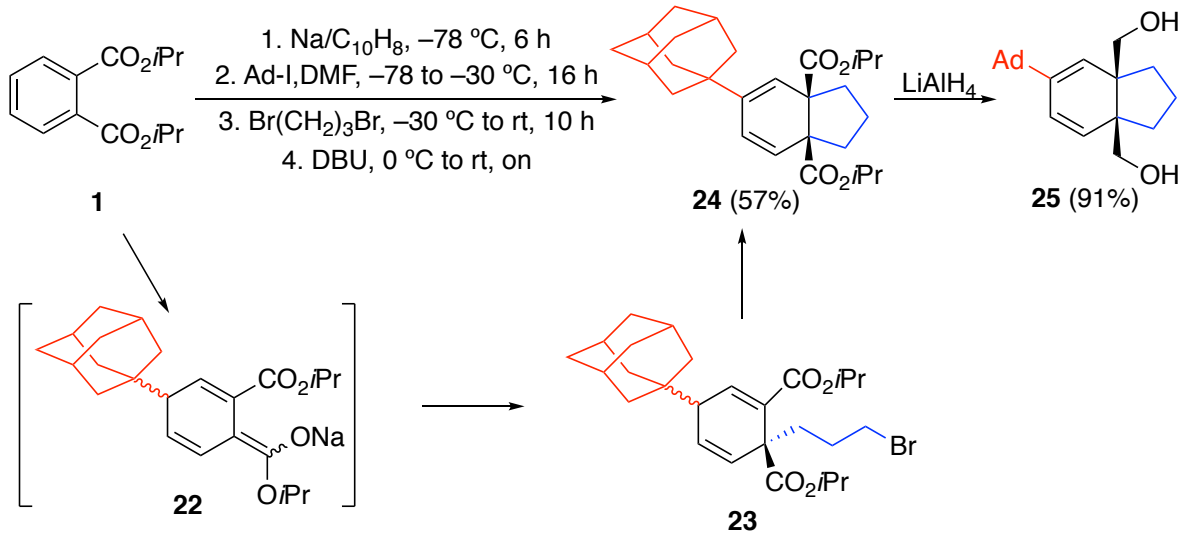
2 **20** **21**

Despite the evidence favoring an $S_{RN}1$, we believe that an S_N2-type mechanism is also operating in these alkylations. The successful outcome of the alkylations reactions with alkyl bromides and tosylates is difficult to attribute to an $S_{RN}1$ mechanism[21] and fit better an S_N2 pathway (table 1). Additionally, we think that reaction at the α-position observed with isopropyl and cycloalkyl halides takes place preferently through an S_N2 mechanism. We believe that the origin of the higher regioselectivity displayed by the reactions of *bis*-enolate **2** with cycloalkyl bromides and tosylates simply reflects the preference of the harder electrophiles (bromides and tosylates) for reacting at the harder α-carbon nucleophilic site of the *bis*-enolate while their softer iodide counterparts display some reactivity towards the softer γ-carbon site, although it could also reflect the preference for $S_{RN}1$ of hindered cycloalkyl iodides. The coexistence of both $S_{RN}1$ and S_N2 mechanisms with secondary electrophiles could also explain the non-stereospecific alkylation of *bis*-enolate **2** with 3-β-iodo-cholest-5-ene, which led to the γ-alkylated product **5g** as a 1.5:1 mixture of β:α epimers at C3, since one expects that the $S_{RN}1$ reaction would be non-stereospecific while the S_N2 reaction would occur with retention of configuration.

Having uncovered the efficient γ-regioselective monoalkylation reaction of *bis*-enolate **2** with highly sterically encumbered electrophiles, and to check if we could further enhance the attractiveness of *bis*-enolates as synthetic intermediates by exploiting their *bis*-nucleophilic nature, we decided to explore if the purported intermediate obtained from the alkylation step, monoenolate **21**, could undergo a subsequent alkylation *in situ* by treatment with an additional, less sterically demanding electrophile. To explore this sequential, two C-

C bond forming transformation we treated *bis*-enolate **2** first with 1-iodoadamantane and then with 1,3-dibromopropane. Under the usual reaction conditions, *bis*-enolate **2** was alkylated with 1-iodoadamantane at the γ-position, then 1,3-dibromopropane was added at –30 ºC and the reaction mixture was stirred for 10 h while warming to rt. At this point we expected that doubly alkylated diester **23** should have formed in the reaction mixture and further reasoned that the removal of the remaining acidic hydrogen of **23** with a suitable base could lead to a cyclization via a third enolate alkylation reaction. In fact, when DBU was added to the reaction mixture obtained as described previously (before quenching) at 0 ºC, the desired adamantyl hydrindadiene **24** was obtained in 57% isolated yield (Scheme 7). The relative configuration of the diester was confirmed to be *cis* by X-Ray crystallography of crystalline diol **25** obtained by $LiAlH_4$ reduction of diester **24**.

Scheme 7. One Pot Sequential Alkylations from Phthalate 1

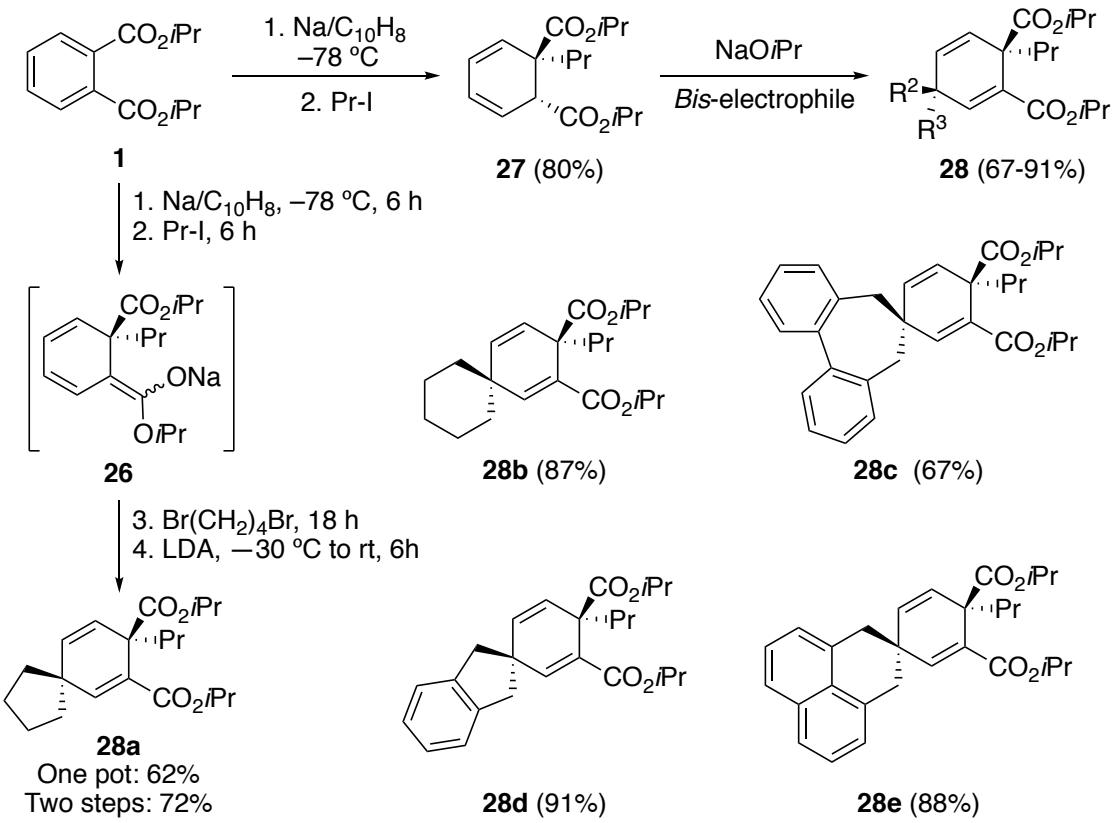


In the same vein of trying to make the most of the versatile, multiple nucleophilic nature of *bis*-enolate **2**, we decided to explore the further alkylation reactions of monoenolate **26**, resulting from the α-selective alkylation of **2** with less sterically demanding electrophiles. We hypothesized that, due to the steric hindrance exerted by the newly introduced α-alkyl group, a second electrophile would react at the γ-carbon of the π-

extended monoenolate. Furthermore, the use of a *bis*-electrophile for the second alkylation process could open a way for a two-step, or maybe even a one-pot, preparation of spirocycles[25] from phthalate **1** (see Scheme 8).

In practice, reductive alkylation of phthalate **1** with 1-iodopropane afforded **27** in 80% yield. Deprotonation of **27** with NaO*i*Pr in THF at –30 ºC generates a dienolate that reacts at the γ-position with 1,4-dibromobutane or with 1,5-dibromopentane to give the five- and six-membered spirocyclic compounds **28a** (90%) and **28b** (87%), respectively. The seven-membered ring homologue could not be obtained from an analogous reaction of **27** with 1,6-dibromohexane.[26] Increasing the rigidity of the electrophile to restrict rotation in the chain proved to be instrumental for the cyclization to occur, and the unsaturated 7-membered spirocycle **28c** was isolated in 67% yield when 2,2′-*bis*(chloromethyl)-1,1′-biphenyl was used as the electrophile. Excellent results were also obtained when *o*-dichloroxylene and 1,8-*bis*(bromomethyl)naphthalene were used, yielding **28d** (91%) and **28e** (88%), respectively. Spirocyclic compounds were also prepared in just one pot from phthalate **1** (see Scheme 8). Sequential alkylation of the *bis*-enolate derived from **1** with 1-iodopropane at -78 ºC for 6 h afforded a monoenolate that was trapped with 1,4-dibromobutane. After stirring at –78 ºC for 18 h, LDA was added at –30 ºC and the reaction mixture was stirred for an additional 6 h while warming to rt. Spiro compound **28a** was isolated after column chromatography in 62% yield, slightly lower than the yield of the two-step procedure (72%). The addition of base is necessary for the dialkylated compound to evolve to the cyclized product.[27]

Scheme 8. Synthesis of Spirocycles



Conclusion

In summary, we have established that *bis*-enolates with extended conjugation prepared by alkaline metal mediated reduction of several aromatic and unsaturated diesters can be regioselectively alkylated with very sterically encumbered electrophiles, including tertiary and neopentyl alkyl halides, in good yields. Additionally, we have, to an extent, delineated (i) the dianionic nature of the nucleophile, (ii) the structural parameters responsible for this nucleophilic behavior, observing that the dianionic nature of these species in conjugation with the extended π-conjugated systems are required for the success of the substitution reactions at extremely sterically hindered electrophilic centers, and (iii) the alkylation mechanism.

The regioselectivity displayed by the studied *bis*-enolates in their reaction with a variety of electrophiles ranged from complete or almost complete α-alkylation in cross-conjugated systems, to complete γ-alkylation in linearly conjugated *bis*-enolate **2** (with

tertiary, hindered secondary and neopentyl halides), or complete α-alkylation with primary, isopropyl and cycloalkyl bromides and tosylates.

As a synthetic application of this reactivity study, we have developed a simple protocol for the direct, one-pot regioselective functionalization of diisopropyl phthalate with bulky substituents, based on the reductive alkylation of phthalate **1** with very hindered tertiary, neopentylic and secondary alkyl halides and the subsequent oxidation of the monoenolate intermediates with oxygen to give 4-alkylphthalates **5**. Additionally, the reactivity of the monoenolate intermediates resulting from these alkylations was put to good synthetic use in developing a protocol for consecutive reductive-alkylation-alkylation protocols which allowed the building of complex fused and spiro-structures from phthalate esters in one-pot or two steps operations.

Experimental Section

General Experimental Methods. All reactions were performed under an inert atmosphere of Argon in flame-dried glassware. Reaction temperatures are reported as the temperature of the bath surrounding the vessel. Solvents were distilled immediately before use: Tetrahydrofuran (THF) from sodium/benzophenone and DMF from CaH_2. Flash column chromatography was performed using Merck silica gel (230-400 mesh) or using a CombiFlash Rf-200 (Teledyne-Isco) with RediSep packed columns. NMR spectra were recorded on a Varian Mercury 300 or a Varian Inova 500 instrument. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent resonance. Melting points (Mp) were determined using a Büchi B-540 apparatus. Infrared spectra were measured using an Agilent Technologies Cary 630 FTIR spectrometer. High-resolution mass spectra were carried out on a Bruker Microtof spectrometer. 1- and 2-Bromoadamantane (Aldrich) were used as received. 1-Iodoadamantene was purified by column chromatography

(SiO_2, hexanes). The other commercial alkyl halides were distilled immediately prior to use. 1-Iodo-1-methylcyclohexane,[28] 6-iodo-2,6-dimethyloctane,[29] 3-iodo-2,2-dimethylbutane[30] and 3-β-iodo-cholestene[31] were prepared by literature procedures.

General Procedure A for the One-Pot Reductive Alkylation of Diisopropyl Phthalate (1) and Rearomatization. A –78 ºC suspension of small pieces of sodium (245 mg, 10.6 mmol) and naphthalene (150 mg, 1.17 mmol) in THF (4 mL) was treated with a solution of **1** (250 μL, 1.06 mmol) in THF (1 mL) and stirred for 6 h. The resulting solution was transferred via cannula to a –78 ºC flask, washed with THF (5 mL) and treated with a solution of the corresponding halide (1.17 mmol, 110 mol%) in DMF (1 mL). The reaction mixture was stirred for 16 h at –30 ºC, cooled down to –78 ºC and oxygen gas was bubbled through the solution for 1h. The reaction mixture was then partitioned between EtOAc (20 mL) and pH 7 buffer solution (15 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution (20 mL) and brine (10 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (SiO_2, 2-5% EtOAc/hexane).

Diisopropyl 4-(adamantan-1-yl)phthalate (5a). Column chromatography afforded **5a** (253 mg, 62% yield) as a white solid when 1-iodoadamantane was used as the electrophile. Mp 130-132 ºC (EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.2 Hz, 1H), 7.60 (d, *J* = 1.9 Hz, 1H), 7.48 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.23 (m, 2H), 2.11 (m, 3H), 1.91 (d, *J* = 3.0 Hz, 6H), 1.78 (m, 6H), 1.37 (d, *J* = 6.3 Hz, 6H), 1.35 (d, *J* = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.1, 166.9, 154.9, 133.3, 129.3, 129.0, 127.3, 125.4, 69.3, 69.0, 43.0, 36.7, 36.7, 28.9, 21.9, 21.9; IR (neat): 1715 cm^{-1} (C=O); HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{24}H_{33}O_4$ 385.2373, found 385.2374.

Diisopropyl 4-(*t*-butyl)phthalate (5b). Column chromatography (2-5% EtOAc/hexane) afforded **5b** (172 mg, 53% yield) as pale yellow oil when *t*-butyl iodide was

used as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 1.9 Hz, 1H), 7.50 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.23 (m, 2H), 1.38 (d, *J* = 6.3 Hz, 6H), 1.36 (d, *J* = 6.3 Hz, 6H), 1.33 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.0, 166.9, 154.8, 133.2, 129.4, 129.0, 127.6, 125.6, 69.3, 69.0, 35.1, 31.1, 21.9, 21.9; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{27}O_4$ 307.1904, found 307.1905.

Diisopropyl 4-(1-methylcyclohexyl)phthalate (5c). Column chromatography (2-5% EtOAc/hexane) afforded **5c** (155 mg, 42% yield) as a pale yellow oil when 1-iodo-1-methylcyclohexane was used as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.49 (dd, *J* = 8.2, 2.1 Hz, 1H), 5.23 (dhept, *J* = 10.0, 6.3 Hz, 2H), 1.98 (m, 2H), 1.64-1.50 (m, 4H), 1.46-1.30 (m, 16H), 1.18 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.0, 166.9, 153.8, 133.3, 129.3, 129.1, 128.3, 126.4, 69.2, 69.0, 38.4, 37.8, 30.3, 26.3, 22.6, 21.9, 21.9; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{21}H_{31}O_4$ 347.2217, found 347.2217.

Diisopropyl 4-(3,7-dimethyloctan-3-yl)phthalate (5d). Column chromatography (2-5% EtOAc/hexane) afforded **5d** (204 mg, 49% yield) as a colorless oil when 6-iodo-2,6-dimethyloctane was used as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, 1H), 7.53 (d, *J* = 2.0 Hz, 1H), 7.39 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.22 (dhept, *J* = 8.8, 6.3 Hz, 2H), 1.81-1.62 (m, 2H), 1.56 (dq, *J* = 14.5, 7.4 Hz, 1H), 1.52-1.39 (m, 2H), 1.36 (d, *J* = 6.2 Hz, 6H), 1.35 (d, *J* = 6.2 Hz, 6H), 1.26 (s, 3H), 1.18-1.03 (m, 3H), 0.91 (m, 1H), 0.78 (dd, *J* = 6.1, 1.4 Hz, 6H), 0.64 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.0, 167.0, 152.0, 133.0, 129.3, 128.8, 128.7, 126.8, 69.2, 68.9, 42.8, 41.6, 39.7, 35.6, 27.8, 23.4, 22.8, 22.6, 21.9, 21.9, 21.8, 8.7; IR (neat): 1722 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{24}H_{39}O_4$ 391.2843, found 391.2845.

Diisopropyl 4-(*t*-pentyl)phthalate (5e). Column chromatography (2-5% EtOAc/hexane) afforded **5e** (200 mg, 59% yield) as colorless oil when 2-bromo-2-

methylbutane was used as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.1 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 1H), 7.44 (dd, *J* = 8.2, 2.0 Hz, 1H), 5.23 (dhept, *J* = 10.9, 6.3 Hz, 2H), 1.66 (q, *J* = 7.4 Hz, 2H), 1.37 (d, *J* = 6.3 Hz, 6H), 1.35 (d, *J* = 6.3 Hz, 6H), 1.29 (s, 6H), 0.67 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.0, 167.0, 153.3, 133.1, 129.3, 128.9, 128.3, 126.3, 69.3, 69.0, 38.4, 36.7, 28.3, 21.9, 21.9, 9.2; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* [M + H]$^{+}$ calcd for $C_{19}H_{29}O_4$ 321.2060, found 321.2063.

Diisopropyl 4-(2,4-dimethylpentan-3-yl)phthalate (5f). Column chromatography (2-5% EtOAc/hexane) afforded **5f** (279 mg, 75% yield) as colorless oil when 3-iodo-2,4-dimethylpentane was used as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.36 (s, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 5.23 (hept, *J* = 6.3 Hz, 2H), 2.23-2.08 (m, 3H), 1.36 (d, *J* = 6.2 Hz, 12H), 0.86 (d, *J* = 6.4 Hz, 6H), 0.72 (d, *J* = 6.4 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.8, 167.2, 145.8, 132.5, 131.9, 130.1, 130.0, 128.3, 69.2, 69.1, 59.4, 28.8, 21.9, 21.9, 21.7, 19.3; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* [M + H]$^{+}$ calcd for $C_{21}H_{33}O_4$ 349.2373, found 349.2377.

3-Iodo-2,4-dimethylpentane. To a 0 ºC solution of PPh_3 (6.74 g, 25.7 mmol), imidazole (1.75 g, 25.7 mmol), and 2,4-dimethylpentan-3-ol (3 mL, 21.4 mmol) in CH_2Cl_2 (107 mL) was added I_2 (6.5 g, 25.6 mmol) and the resulting mixture was stirred at rt for 16 h. H_2O (25 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (20 mL), and the organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (SiO_2, 100% hexane) to yield 3-iodo-2,4-dimethylpentane (2.27 g, 47%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (t, *J* = 6.1 Hz, 1H), 1.55 (h, *J* = 6.5 Hz, 2H), 1.02 (d, *J* = 6.4 Hz, 1H), 0.98 (d, *J* = 6.6 Hz, 1H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 64.4, 33.3, 23.1, 22.7.

Diisopropyl 4-((8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-dimethyl-17-((*R*)-4-methylpentan-2-yl)-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-

3-yl)phthalate (5g). Column chromatography afforded **5g** (349 mg, 53% yield) as pale yellow oil and as 1.5:1 mixture of epimers when 3-β-iodocholest-5-ene was used as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ (minor + major) 7.69 and 7.47 (d, *J* = 1.8 Hz, 1H), 7.60 and 7.66 (d, *J* = 8.0 Hz, 1H), 7.51 and 7.35 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.46 and 5.36 (m, 1H), 5.23 (m, 2H), 3.13 and 2.58 (m, 1H), 2.42 (m, 1H), 2.80 and 2.17 (m, 1H), 2.06-1.94 (m, 3H), 1.89-1.69 (m 3H), 1.62-0.84 (m, 35H), 0.93 and 0.90 (d, *J* = 6.5 Hz, 3H), 0.87 (m, 6H), 0.70 and 0.68 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ (minor + major) 167.9, 167.7, 167.2, 166.8, 150.7, 150.2, 142.3, 140.9, 133.6, 132.6, 130.6, 129.8, 129.5, 129.3, 128.9, 128.8, 128.6, 127.1, 122.3, 120.8, 69.3, 69.0, 69.0, 68.9, 57.0, 56.9, 56.3, 56.3, 50.6, 49.9, 45.8, 42.4, 40.3, 39.9, 39.8, 39.8, 39.7, 39.6, 38.5, 37.4, 37.0, 36.3, 36.0, 35.9, 35.4, 32.9, 32.1, 32.0, 32.0, 31.9, 29.8, 28.4, 28.4, 28.1, 28.1, 24.4, 24.4, 24.0, 24.0, 23.0, 22.7, 22.0, 21.9, 21.9, 21.1, 20.8, 19.8, 19.7, 18.9, 18.8, 12.0, 12.0; IR (neat): 1722 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{41}H_{62}O_4Na$ 641.4540, found 641.4544.

Diisopropyl 4-neopentylphthalate (5h). Column chromatography afforded **5h** (217 mg, 64% yield) as colorless oil when 1-iodo-2,2-dimethylpropane was used as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 7.9 Hz, 1H), 7.37 (d, *J* = 1.7 Hz, 1H), 7.23 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.22 (m, 2H), 2.53 (s, 2H), 1.34 (dd, *J* = 6.4, 2.5 Hz, 12H), 0.89 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.7, 167.0, 143.4, 132.7, 132.5, 130.4, 129.8, 128.5, 69.1, 69.0, 49.9, 32.0, 29.3, 21.9, 21.8; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{19}H_{29}O_4$ 321.2060, found 321.2061.

Diisopropyl 4-(3,3-dimethylbutan-2-yl)phthalate (5i). Column chromatography afforded **5i** (227 mg, 64% yield) as colorless oil when 3-iodo-2,2-dimethylbutane was used as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 1.7 Hz, 1H), 7.28 (dd, *J* = 8.0, 1.7 Hz, 1H), 5.23 (dhept, *J* = 12.9, 6.5 Hz, 2H), 2.62 (q, *J* = 7.1 Hz, 1H), 1.36 (dd, *J* = 6.3, 4.2 Hz, 12H), 1.25 (d, *J* = 7.2 Hz, 3H), 0.86 (s, 9H); ^{13}C{^{1}H}

NMR (126 MHz, $CDCl_3$) δ 167.7, 166.9, 148.9, 132.5, 131.0, 129.8, 129.2, 128.3, 69.1, 68.9, 49.9, 33.8, 27.7, 21.8, 21.8, 21.8, 15.6; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{20}H_{31}O_4$ 335.2217, found 335.2219.

General Procedure B for the Reductive Alkylation of Diisopropyl Phthalate (1) with Secondary Halides. Preparation of Kinetic Isomer 3. A –78 ºC suspension of small pieces of sodium (245 mg, 10.6 mmol) and naphthalene (150 mg, 1.17 mmol) in THF (4 mL) was treated with a solution of **1** (250 μL, 1.06 mmol) in THF (1 mL) and stirred for 6 h. The resulting solution was transferred via cannula to a –78 ºC flask, washed with THF (5 mL) and treated with a solution of the corresponding secondary halide (1.17 mmol) in DMF (1 mL). The reaction mixture was slowly warmed to –30 ºC and stirred for 16 h, quenched by addition of deoxygenated HOAc (150 μL, 2.62 mmol) and stirred for 1 min. The reaction mixture was partitioned between EtOAc (20 mL) and pH 7 buffer solution (15 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution (20 mL) and brine (10 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (SiO_2, 2-5% EtOAc/hexane).

Diisopropyl *trans*-1-isopropylcyclohexa-3,5-diene-1,2-dicarboxylate (**3a**). Colorless oil, 80% yield (250 mg) using 2-bromopropane as the electrophile. ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (dd, *J* = 9.7, 5.1 Hz, 1H), 5.91 (m, 1H), 5.81 (dd, *J* = 9.4, 4.8 Hz, 1H), 5.73 (d, *J* = 9.6 Hz, 1H), 5.01 (m, 2H), 3.97 (dd, *J* = 4.8, 2.0 Hz, 1H), 2.37 (hept, *J* = 6.9 Hz, 1H), 1.23 (d, *J* = 6.4 Hz, 6H), 1.21 (d, *J* = 6.3 Hz, 6H), 0.98 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.6, 170.9, 128.1, 124.7, 124.4, 123.6, 68.4, 68.0, 52.2, 46.0, 32.0, 22.0, 21.8, 21.8, 21.7, 18.8, 17.9; IR (neat): 1722 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{27}O_4$ 295.1904, found 295.1902.

Diisopropyl *trans*-1-cyclobutylcyclohexa-3,5-diene-1,2-dicarboxylate (**3b**). Colorless oil, 86% yield (279 mg) using bromocyclobutane as the electrophile. ^{1}H NMR (500 MHz, C_6D_6) δ 5.99 (dd, *J* = 9.7, 3.2 Hz, 1H), 5.92 (dd, *J* = 9.7, 5.2 Hz, 1H), 5.69 (m, 1H), 5.58 (dd, *J* = 9.7, 1.1 Hz, 1H), 5.00 (dhept, *J* = 25.1, 6.3 Hz, 2H), 4.36 (t, *J* = 3.2 Hz, 1H), 3.09 (tt, *J* = 10.4, 7.7 Hz, 1H), 2.11 (m, 3H), 1.95 (m, 1H), 1.73 (qt, *J* = 10.4, 8.1 Hz, 1H), 1.61 (m, 1H), 1.07 (m, 9H), 1.01 (d, *J* = 6.3 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, C_6D_6) δ 174.0, 170.9, 126.4, 125.0, 124.7, 123.6, 68.2, 68.1, 50.6, 47.0, 39.2, 25.5, 25.3, 21.9, 21.8, 21.7, 21.7, 19.2; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{27}O_4$ 307.1904, found 307.1905.

Diisopropyl *trans*-1-cyclopentylcyclohexa-3,5-diene-1,2-dicarboxylate (**3c**). Colorless oil, 84% yield (285 mg) using bromocyclopentane as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.02 (dd, *J* = 9.7, 5.1 Hz, 1H), 5.92 (ddd, *J* = 9.7, 5.1, 2.2 Hz, 1H), 5.85 (dd, *J* = 9.6, 4.1 Hz, 1H), 5.71 (d, *J* = 9.7 Hz, 1H), 5.02 (dhept, *J* = 16.3, 6.3 Hz, 2H), 4.05 (dd, *J* = 4.1, 2.3 Hz, 1H), 2.36 (tt, *J* = 9.6, 7.4 Hz, 1H), 1.72 (m, 2H), 1.58-1.34 (m, 6H), 1.23 (dt, *J* = 8.4, 6.2 Hz, 12H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.3, 171.3, 127.6, 124.4, 123.9, 68.5, 68.2, 51.3, 47.3, 43.7, 28.5, 27.2, 25.3, 25.0, 22.0, 21.9, 21.8, 21.8; IR (neat): 1715 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{19}H_{29}O_4$ 321.2060, found 321.2060.

Diisopropyl *trans*-[1,1'-bi(cyclohexane)]-3,5-diene-1,2-dicarboxylate (3d). Colorless oil, 79% yield (279 mg) using bromocyclohexane as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (dd, *J* = 9.7, 5.1 Hz, 1H), 5.90 (ddd, *J* = 9.7, 5.1, 1.9 Hz, 1H), 5.80 (dd, *J* = 9.5, 4.8 Hz, 1H), 5.76 (d, *J* = 9.7 Hz, 1H), 5.01 (dhept, *J* = 12.5, 6.3 Hz, 2H), 3.96 (dd, *J* = 4.8, 2.0 Hz, 1H), 1.98 (m, 2H), 1.75-1.56 (m, 4H), 1.28-1.14 (m, 15H), 1.13-0.98 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, 60 ºC, $CDCl_3$) δ 173.8, 170.9, 128.4, 124.7, 124.6,

123.3, 68.4, 68.0, 52.6, 46.1, 43.0, 29.2, 28.0, 27.2, 27.0, 26.7, 22.0, 21.8, 21.8; IR (neat): 1722 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{20}H_{31}O_4$ 335.2217, found 335.2219.

Diisopropyl *trans*-1-cycloheptylcyclohexa-3,5-diene-1,2-dicarboxylate (3e). Colorless oil, 83% yield (307 mg) using bromocycloheptane as the electrophile. ^1H NMR (500 MHz, $CDCl_3$) δ 5.95 (dd, *J* = 9.7, 5.1 Hz, 1H), 5.88 (ddd, *J* = 9.7, 5.1, 1.9 Hz, 1H), 5.76 (dd, *J* = 9.4, 5.0 Hz, 1H), 5.70 (d, *J* = 9.7 Hz, 1H), 4.97 (dhept, *J* = 14.0, 6.3 Hz, 2H), 3.94 (dd, *J* = 5.0, 2.0 Hz, 1H), 2.13 (tt, *J* = 10.1, 2.9 Hz, 1H), 1.92 (m, 1H), 1.63 (m, 3H), 1.55-1.30 (m, 7H), 1.25 (m, 1H), 1.19 (dt, *J* = 12.1, 6.1 Hz, 12H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.9, 170.8, 128.8, 124.8, 124.3, 123.4, 68.3, 67.9, 53.0, 45.8, 43.4, 29.4, 29.3, 27.8, 27.6, 27.6, 27.5, 21.8, 21.7, 21.7, 21.7; IR (neat): 1722 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{21}H_{33}O_4$ 349.2373, found 349.2375.

Diisopropyl *trans*-1-cyclooctylcyclohexa-3,5-diene-1,2-dicarboxylate (3f). Colorless oil, 80% yield (307 mg) using bromocyclooctane as the electrophile. ^1H NMR (500 MHz, $CDCl_3$) δ 5.99 (ddd, *J* = 9.7, 5.1, 1.0 Hz, 1H), 5.92 (ddd, *J* = 9.5, 5.0, 1.9 Hz, 1H), 5.80 (dd, *J* = 9.4, 5.0 Hz, 1H), 5.72 (d, *J* = 9.7 Hz, 1H), 5.00 (dhept, *J* = 15.4, 6.3 Hz, 2H), 3.97 (dd, *J* = 5.1, 1.9 Hz, 1H), 2.31 (tt, *J* = 9.2, 2.9 Hz, 1H), 1.86 (m, 1H), 1.72-1.27 (m, 13H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.22 (dd, *J* = 6.2, 1.7 Hz, 6H), 1.20 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 174.1, 170.9, 129.0, 125.0, 124.6, 123.7, 68.5, 68.1, 53.8, 45.8, 41.0, 29.1, 29.0, 27.2, 26.6, 26.6, 26.2, 26.1, 22.0, 21.9, 21.9, 21.8; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{35}O_4$ 363.2530, found 363.2523.

Diisopropyl *trans*-1-(tetrahydro-2*H*-pyran-4-yl)cyclohexa-3,5-diene-1,2-dicarboxylate (3g). Colorless oil, 43% yield (152 mg) using 4-bromotetrahydropyran as the electrophile. ^1H NMR (500 MHz, $CDCl_3$) δ 6.04 (ddd, *J* = 9.8, 5.1, 1.0 Hz, 1H), 5.91 (dddd, *J* = 9.5, 5.1, 2.4, 0.8 Hz, 1H), 5.80 (ddt, *J* = 9.5, 4.1, 1.0 Hz, 1H), 5.69 (dt, *J* = 9.8, 0.9 Hz, 1H), 5.03 (dhept, *J* = 9.3, 6.3 Hz, 2H), 4.04 (dd, *J* = 4.1, 2.4 Hz, 1H), 3.93 (m, 2H), 3.32 (m,

2H), 2.28 (tt, *J* = 11.7, 3.5 Hz, 1H), 1.76 (dp, *J* = 13.2, 2.3 Hz, 1H), 1.63-1.41 (m, 3H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.24 (dd, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.22 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 173.6, 171.0, 126.5, 124.4, 124.3, 123.9, 68.8, 68.5, 68.4, 68.3, 51.8, 46.1, 40.3, 29.3, 27.6, 21.9, 21.9, 21.8, 21.8; IR (neat): 1730 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{19}H_{29}O_5$ 337.2010, found 337.2010.

Diisopropyl *trans*-1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)cyclohexa-3,5-diene-1,2-dicarboxylate (3h). Colorless oil, 76% yield (350 mg) using 1-Boc-4-bromopiperidine as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.03 (ddd, *J* = 9.8, 5.1, 1.1 Hz, 1H), 5.91 (ddd, *J* = 9.6, 4.9, 2.3 Hz, 1H), 5.85 (dd, *J* = 9.5, 3.9 Hz, 1H), 5.67 (d, *J* = 9.8 Hz, 1H), 5.03 (m, 2H), 4.23-3.84 (m, 3H), 2.58 (m, 2H), 2.16 (tt, *J* = 12.2, 3.0 Hz, 1H), 1.85 (dt, *J* = 13.2, 2.8 Hz, 1H), 1.60 (m, 1H), 1.42 (s, 9H), 1.35 (qd, *J* = 12.5, 4.3 Hz, 1H), 1.30-1.16 (m, 13H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 173.7, 171.0, 154.9, 126.6, 124.5, 124.3, 124.0, 79.4, 68.9, 68.5, 51.9, 46.3, 44.5, 41.4, 28.6, 28.4, 26.8, 22.0, 21.8, 21.8, 21.8; IR (neat): 1730, 1692 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{24}H_{37}NO_6Na$ 458.2513, found 458.2514.

Diisopropyl 4-cyclohexylphthalate (5j). Silica gel purification of **4d** rendered the rearomatized product **5j** (R = Cyclohexyl, 25 mg, 7%) as a colorless oil when using iodocyclohexane as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.16 (dhept, *J* = 12.6, 6,3 Hz, 2H), 2.49 (ddd, *J* = 11.7, 8.4, 3.2 Hz, 1H), 1.79 (m, 4H), 1.69 (d, *J* = 13.1 Hz, 1H), 1.40-1.25 (m, 16 H), 1.18 (m, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 167.9, 166.9, 151.6, 133.5, 129.7, 129.3, 129.0, 127.2, 69.2, 69.0, 44.6, 34.2, 26.8, 26.1, 21.9, 21.9; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{20}H_{29}O_4$ 333.2060, found 333.2062.

Diisopropyl 4-cycloheptylphthalate (5k). Silica gel purification of **4e** rendered the rearomatized product **5k** (R = Cycloheptyl, 77 mg, 21%) as a colorless oil when using

iodocycloheptane as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 7.30 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.22 (dhept, *J* = 12.6, 6.3 Hz, 2H), 2.71 (tt, *J* = 10.6, 3.6 Hz, 1H), 1.93-1.47 (m, 12H), 1.36 (d, *J* = 6.3 Hz, 6H), 1.34 (d, *J* = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 167.9, 166.9, 153.5, 133.5, 129.4, 129.3, 128.8, 127.0, 69.2, 69.0, 47.0, 36.5, 27.9, 27.3, 21.9, 21.9; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{21}H_{31}O_4$ 347.2217, found 347.2216.

Diisopropyl 4-cyclooctylphthalate (5l). Silica gel purification of **4f** rendered the rearomatized product **5l** (R = Cyclooctyl, 80 mg, 21%) as a colorless oil when using iodocyclooctane as the electrophile. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 1.8 Hz, 1H), 7.30 (dd, *J* = 8.0, 1.8 Hz, 1H), 5.23 (dhept, *J* = 12.5, 6.3 Hz, 2H), 2.82 (m, 1H), 1.85-1.53 (m, 14H), 1.37 (d, *J* = 6.3 Hz, 6H), 1.35 (d, *J* = 6.3 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 168.0, 166.9, 154.0, 133.5, 129.4, 129.3, 129.1, 127.3, 69.3, 69.0, 44.7, 34.5, 26.9, 26.4, 26.0, 21.9, 21.9; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{33}O_4$ 361.2373, found 361.2375.

***Bis*(4-bromobenzoate) 6**. A solution of **3d** (495 mg, 1.48 mmol) in THF (4.8 mL) was slowly added to a 0 ºC suspension of $LiAlH_4$ (124 mg, 3.26 mmol) in THF (10 mL). The reaction mixture was stirred at rt for 24 h. After cooling at 0 ºC, EtOAc (0.5 mL) was slowly added, followed by $CHCl_3$ (2 mL), sat Na_2CO_3 (1 mL), KH_2PO_4, and Na_2SO_4. The resulting mixture was stirred at rt for 1h, filtered over celite, and the solid washed with $CHCl_3$ (10 mL). The combined clear filtrate and washings were evaporated to give a colorless residue (316 mg) that was dissolved in CH_2Cl_2 (14 mL), DMAP (35 mg, 0.28 mmol) and Et_3N (475 μL, 3.4 mmol) were added, and the reaction mixture was cooled to 0 ºC, treated with *p*-bromobenzoyl chloride (750 mg, 3.4 mmol) and stirred for 24 h at rt. The reaction mixture was quenched with saturated NH_4Cl (5 mL) and then partitioned between CH_2Cl_2 (15 mL) and pH 7 phosphate buffer (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 10

mL), and the combined organic layers were dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (SiO_2, 5% EtOAc/hexane) to yield the product as a white solid (683 mg, 78% yield from **3d**). Suitable crystals for X-ray analyses were obtained by recrystallization from a mixture *i*PrOH/dioxane (1:2). Mp 116-119 ºC (*i*PrOH/dioxane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (dd, *J* = 8.2, 5.8 Hz, 4H), 7.57 (dd, *J* = 11.3, 8.2 Hz, 4H), 6.08 (dd, *J* = 9.9, 5.0 Hz, 1H), 5.93 (dd, *J* = 10.1, 4.9 Hz, 1H), 5.85 (dd, *J* = 9.6, 4.0 Hz, 1H), 5.58 (d, *J* = 9.8 Hz, 1H), 4.65 (dd, *J* = 10.7, 5.2 Hz, 1H), 4.47-4-33 (m, 3H), 3.23 (dt, *J* = 9.4, 4.6 Hz, 1H), 1.98 (d, *J* = 12.5 Hz, 1H), 1.80 (m, 3H), 1.66 (d, *J* = 11.8 Hz, 1H), 1.53 (t, *J* = 11.6 Hz, 1H), 1.37-1.04 (m, 5H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 166.1, 165.8, 132.0, 131.9, 131.2, 129.3, 129.1, 129.1, 128.4, 128.3, 128.3, 126.0, 123.9, 67.9, 64.8, 43.0, 42.7, 37.8, 28.8, 27.5, 27.3, 27.1, 26.7; IR (neat): 1711 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + Na]^+$ calcd for $C_{28}H_{28}Br_2O_4Na$ 609.0247, found 609.0241.

Alkylation with Secondary Bromides and Quenching with *i*PrOH: Preparation of Thermodynamic Isomers 7. General procedure B was followed and the reaction mixture was quenched, after being stirred with the electrophile for 16 h at –30 ºC, by addition of deoxygenated *i*PrOH (200 μl, 2.65 mmol), stirred for 3 h at the same temperature, and worked-up as described for **3**.

Diisopropyl 1-isopropylcyclohexa-2,4-diene-1,2-dicarboxylate (**7a**). Colorless oil (237 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (ddd, *J* = 4.5, 3.0, 1.4 Hz, 1H), 5.90 (m, 1H), 5.61 (dt, *J* = 10.0, 2.0 Hz, 1H), 5.03 (hept, *J* = 6.3 Hz, 1H), 4.95 (hept, *J* = 6.3 Hz, 1H), 2.88 (dtd, *J* = 24.2, 4.1, 1.6 Hz, 1H), 2.79 (dq, *J* = 24.2, 2.8 Hz, 1H), 2.68 (hept, *J* = 6.8 Hz, 1H), 1.24 (dd, *J* = 6.3, 4.6 Hz, 6H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 1.07 (d, *J* = 6.8 Hz, 3H), 0.70 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 173.3, 166.0, 137.2, 131.7, 125.9, 124.6, 68.0, 67.9, 52.2, 33.0, 27.3, 21.9, 21.8, 21.6, 19.2,

18.8; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{27}O_4$ 295.1904, found 295.1904.

Diisopropyl 1-cyclobutylcyclohexa-2,4-diene-1,2-dicarboxylate (**7b**). Colorless oil (276 mg, 85% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (ddd, *J* = 4.3, 3.1, 1.5 Hz, 1H), 5.93 (dddd, *J* = 10.1, 3.8, 2.9, 1.5 Hz, 1H), 5.63 (ddd, *J* = 10.1, 2.4, 1.6 Hz, 1H), 4.98 (hept, *J* = 6.3 Hz, 1H), 4.89 (hept, *J* = 6.3 Hz, 1H), 3.23 (tt, *J* = 9.7, 7.9 Hz, 1H), 2.86 (dtd, *J* = 24.3, 4.0, 1.6 Hz, 1H), 2.78 (dq, *J* = 24.3, 2.9 Hz, 1H), 1.96 (m, 2H), 1.68 (m, 1H), 1.57-1.38 (m, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.19 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.10 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.5, 165.3, 137.4, 130.0, 126.3, 124.9, 67.8, 67.7, 50.5, 41.1, 27.5, 24.3, 23.7, 21.8, 21.8, 21.7, 21.5, 17.9; IR (neat): 1715 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{27}O_4$ 307.1904, found 307.1905.

Diisopropyl 1-cyclopentylcyclohexa-2,4-diene-1,2-dicarboxylate (**7c**). Colorless oil (265 mg, 78% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.05 (ddd, *J* = 4.4, 3.1, 1.4 Hz, 1H), 5.91 (dtd, *J* = 10.1, 3.4, 1.4 Hz, 1H), 5.67 (dt, *J* = 10.1, 2.0 Hz, 1H), 5.04 (hept, *J* = 6.3 Hz, 1H), 4.97 (hept, *J* = 6.3 Hz, 1H), 2.84 (m, 3H), 2.00 (m, 1H), 1.59-1.32 (m, 6H), 1.25 (dd, *J* = 6.2, 3.3 Hz, 6H), 1.19 (d, *J* = 6.3 Hz, 3H), 1.16 (d, *J* = 6.3 Hz, 3H), 0.98 (m, 1H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.8, 165.8, 136.7, 132.2, 125.9, 124.9, 68.0, 67.9, 51.1, 45.1, 29.0, 27.8, 27.5, 26.0, 24.8, 21.9, 21.9, 21.8, 21.6; IR (neat): 1715 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{19}H_{29}O_4$ 321.2060, found 321.2060.

Diisopropyl [1,1'-bi(cyclohexane)]-2,4-diene-1,2-dicarboxylate (**7d**). Colorless oil (266 mg, 75% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (t, *J* = 4.0 Hz, 1H), 5.86 (d, *J* = 10.0 Hz, 1H), 5.63 (dt, *J* = 10.0, 2.1 Hz, 1H), 5.03 (hept, *J* = 6.3 Hz, 1H), 4.95 (hept, *J* = 6.3 Hz, 1H), 2.86 (dt, *J* = 24.2, 4.4 Hz, 1H), 2.77 (dd, *J* = 24.1, 2.9 Hz, 1H), 2.32 (tt, *J* = 12.1, 3.0 Hz, 1H), 2.19 (m, 1H), 1.80-1.42 (m, 4H), 1.28 (m, 2H), 1.25 (dd, *J* = 6.3, 3.2 Hz, 6H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.14 (d, *J* = 6.3 Hz, 3H), 1.02 (m, 2H), 0.79 (qd, *J* = 12.7, 3.6 Hz,

1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 173.3, 166.1, 137.2, 131.4, 127.1, 123.9, 67.9, 67.9, 52.4, 43.8, 29.1, 29.0, 27.3, 27.1, 26.7, 21.9, 21.8, 21.6; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{20}H_{31}O_4$ 335.2217, found 335.2217.

Diisopropyl 1-cycloheptylcyclohexa-2,4-diene-1,2-dicarboxylate (**7e**). Colorless oil (306 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (ddd, *J* = 4.2, 3.2, 1.5 Hz, 1H), 5.88 (dtd, *J* = 10.2, 3.3, 1.5 Hz, 1H), 5.68 (dt, *J* = 10.2, 2.0 Hz, 1H), 5.06 (hept, *J* = 6.2 Hz, 1H), 4.98 (hept, *J* = 6.3 Hz, 1H), 2.89 (dtd, *J* = 24.3, 3.9, 1.7 Hz, 1H), 2.81 (dtd, *J* = 24.2, 3.1, 2.2 Hz, 1H), 2.58 (m, 1H), 2.03 (m, 1H), 1.78 (m, 1H), 1.64 (m, 1H), 1.48 (m, 6H), 1.29-1.14 (m, 14H), 1.03 (m, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 173.3, 166.2, 137.1, 131.9, 126.3, 124.3, 68.0, 67.9, 53.6, 43.4, 30.8, 29.8, 29.4, 28.4, 27.3, 27.3, 27.0, 21.9, 21.8, 21.6; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{21}H_{33}O_4$ 349.2373, found 349.2375.

Diisopropyl 1-cyclooctylcyclohexa-2,4-diene-1,2-dicarboxylate (**7f**). Colorless oil (292 mg, 76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (m, 1H), 5.88 (d, *J* = 10.1 Hz, 1H), 5.66 (dd, *J* = 10.3, 2.0 Hz, 1H), 5.05 (hept, *J* = 6.3 Hz, 1H), 4.97 (hept, *J* = 6.3 Hz, 1H), 2.88 (dtd, *J* = 24.2, 3.9, 1.8 Hz, 1H), 2.79 (m, 1H), 2.70 (m, 1H), 1.97 (dt, *J* = 13.9, 4.7 Hz, 1H), 1.79-1.13 (m, 24H), 1.06 (m, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 173.4, 166.3, 137.3, 132.0, 126.0, 124.7, 68.0, 68.0, 54.3, 40.9, 31.1, 29.3, 29.0, 27.4, 27.3, 27.2, 25.7, 23.9, 21.9, 21.8, 21.7; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{35}O_4$ 363.2530, found 363.2530.

Diisopropyl 1-(tetrahydro-2*H*-pyran-4-yl)cyclohexa-2,4-diene-1,2-dicarboxylate (**7g**). Colorless oil (162 mg, 45% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 (ddd, *J* = 4.5, 3.0, 1.5 Hz, 1H), 5.92 (dddd, *J* = 10.1, 4.1, 2.7, 1.4 Hz, 1H), 5.61 (ddd, *J* = 10.1, 2.5, 1.5 Hz, 1H), 5.04 (hept, *J* = 6.3 Hz, 1H), 4.96 (hept, *J* = 6.3 Hz, 1H), 3.94 (m, 2H), 3.39 (dtd, *J* = 25.9, 11.8, 2.2 Hz, 2H), 2.90 (dtd, *J* = 24.3, 4.2, 1.5 Hz, 1H), 2.80 (dq, *J* = 24.3, 2.8 Hz, 1H),

2.58 (tt, *J* = 12.2, 3.4 Hz, 1H), 2.13 (dt, *J* = 13.0, 2.7 Hz, 1H), 1.47 (qd, *J* = 12.3, 4.2 Hz, 1H), 1.32 (m, 1H), 1.26 (dd, *J* = 6.2, 3.5 Hz, 6H), 1.18 (m, 1H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 173.0, 165.7, 138.1, 130.5, 126.5, 124.8, 68.6, 68.5, 68.2, 51.6, 41.3, 29.2, 29.0, 27.4, 22.0, 21.9, 21.8, 21.6; IR (neat): 1729, 1707 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{19}H_{29}O_5$ 337.2010, found 337.2010.

Diisopropyl 1-(1-(*tert*-butoxycarbonyl)piperidin-4-yl)cyclohexa-2,4-diene-1,2-dicarboxylate (**7h**). Colorless oil (252 mg, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (t, *J* = 3.7 Hz, 1H), 5.87 (d, *J* = 9.9 Hz, 1H), 5.55 (d, *J* = 10.1 Hz, 1H), 5.01 (hept, *J* = 6.3 Hz, 1H), 4.93 (hept, *J* = 6.3 Hz, 1H), 4.06 (m, 2H), 2.93-2.53 (m, 4H), 2.42 (m, 1H), 2.18 (br d, *J* = 12.9 Hz, 1H), 1.40 (s, 9H), 1.29-1.08 (m, 14H), 0.96 (m, 1H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 172.9, 165.7, 154.8, 138.0, 130.6, 126.3, 124.7, 79.2, 68.1, 68.1, 51.5, 44.3, 42.2, 28.5, 28.2, 28.0, 27.2, 21.9, 21.9, 21.7, 21.5; IR (neat): 1730, 1692 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{24}H_{38}NO_6$ 436.2694, found 436.2695.

Dimethyl 9-(*t*-butyl)-9,10-dihydroanthracene-9,10-dicarboxylate (10). A suspension of small and thin pieces of sodium (156 mg, 6.8 mmol) and naphthalene (192 mg, 1.5 mmol) in THF (5 mL) was sonicated for 45 min to rt. The dark purple solution was transferred via cannula to a flask under Ar, and the excess sodium was washed with THF (0.8 mL). The vessel was cooled to −78 ºC and a solution of anthracene **8** (200 mg, 0.68 mmol) in THF (1 mL) was added. After 3 h, *t*-butyl iodide (90 μL, 0.75 mmol) was added, and the resulting mixture was stirred for 16 h while slowly warming to rt. The reaction was quenched with deoxygenated HOAc (100 μL, 1.75 mmol), pH 7 phosphate buffer was added (10 mL), and the mixture extracted with EtOAc (10 mL). The aqueous phase was extracted with EtOAc (2 x 5 mL) and the combined organic phase was washed with 10% aqueous $Na_2S_2O_3$ solution (10 mL) and brine (10 mL), dried, filtered and evaporated. The residue was

purified by flash column chromatography (SiO_2, 2-5% EtOAc/hexane) to give 110 mg of **10** as a white solid (46% yield). Mp 166-169 ºC (EtOAc-Hex); ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.54 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.34 (td, *J* = 7.5, 1.4 Hz, 2H), 7.27 (td, *J* = 7.6, 1.5 Hz, 2H), 7.10 (dd, *J* = 8.0, 1.4 Hz, 2H), 5.08 (s, 1H), 3.64 (s, 3H), 3.45 (s, 3H), 0.94 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 175.0, 172.1, 136.3, 132.4, 131.6, 130.1, 126.6, 126.1, 62.9, 52.7, 51.9, 50.6, 39.9, 27.4; IR (neat): 1726 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{25}O_4$ 353.1747, found 353.1745.

Alkylation of Diisopropyl Naphthalene-1,4-dicarboxylate (11a) with *t*-Butyl Iodide. A suspension of small pieces of sodium (190 mg, 8.3 mmol) and naphthalene (235 mg, 1.83 mmol) in THF (5 mL) was sonicated for 45 min at rt. The dark purple solution was transferred via cannula to a flask under Ar, and the excess sodium was washed with THF (3 mL). The vessel was cooled to –50 ºC and a solution of naphthalene **11a** (250 mg, 0.83 mmol) in THF (1 mL) was added, stirred for 6 h, and treated with *t*-butyl iodide (110 μL, 0.92 mmol). The reaction mixture was slowly warmed to –30 ºC and stirred for 16 h, quenched by addition of deoxygenated HOAc (120 μL, 2.1 mmol). The reaction mixture was partitioned between EtOAc (10 mL) and pH 7 buffer solution (10 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution (20 mL) and brine (10 mL), dried (anhydrous Na_2SO_4), filtered and evaporated. The residue was purified by flash column chromatography (15-42 μm SiO_2, 50-70% CH_2Cl_2/hexane) to give **13** (155 mg, 52%) and **14** (86 mg, 29%) as colorless oils.

Diisopropyl 1-(*t*-butyl)-1,4-dihydronaphthalene-1,4-dicarboxylate (13). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.34 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.25 (td, *J* = 7.4, 1.4 Hz, 1H), 7.21 (td, *J* = 7.6, 1.7 Hz, 1H), 6.17 (m, 2H), 5.02 (dhept, *J* = 9.6, 6.3 Hz, 2H), 4.37 (d, *J* = 3.5 Hz, 1H), 1.22 (m, 9H), 1.11 (d, *J* = 6.3 Hz, 3H), 1.01 (s, 9H);

$^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ 173.0, 171.3, 134.0, 132.5, 130.5, 129.9, 129.9, 126.5, 125.8, 122.8, 68.8, 68.3, 57.2, 46.4, 39.5, 27.6, 21.8, 21.8, 21.8, 21.5; IR (neat): 1722 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{31}O_4$ 359.2217, found 359.2211.

Diisopropyl 2-(*t*-butyl)-1,2-dihydronaphthalene-1,4-dicarboxylate (14). Mixture of *cis-trans* isomers (1.0: 1.4), ^{1}H NMR (500 MHz, $CDCl_3$) δ (minor + major) 7.83 and 7.81 (2d, *J* = 7.8 Hz, 1H), 7.30-7.15 (m, 3H), 7.09 (dd, *J* = 3.2, 1.3 Hz, 0.6H) and 6.99 (dd, *J* = 6.5, 1.1 Hz, 0.4H), 5.22 (hept, *J* = 6.2 Hz, 0.6H) and 5.19 (hept, *J* = 6.2 Hz, 0.4H) , 4.88 (hept, *J* = 6.2 Hz, 0.4H) and 4.81 (hept, *J* = 6.2 Hz, 0.6H), 3.81 (s, 0.4H) and 3.77 (dd, *J* = 6.2, 1.3 Hz, 0.6H), 2.77 (dd, *J* = 6.5, 1.3 Hz, 0.4H) and 2.61 (dd, *J* = 6.1, 3.1 Hz, 0.6H), 1.35 (m, 6H), 1.07 (m, 12H), 0.85 (s, 3H); $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$) δ (major + minor) 172.9, 171.7, 166.2, 166.0, 139.6, 139.0, 135.4, 133.2, 131.7, 131.3, 130.9, 130.3, 129.4, 127.9, 127.7, 127.7, 127.5, 127.2, 126.1, 68.5, 68.2, 68.1, 68.0, 49.0, 46.9, 46.3, 45.7, 36.2, 32.7, 28.4, 27.7, 22.1, 22.1, 22.0, 21.8, 21.7, 21.6, 21.5; IR (neat): 1715 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{22}H_{31}O_4$ 359.2217, found 359.2214.

Dimethyl 1-(*t*-butyl)-1,2-dihydronaphthalene-1,4-dicarboxylate (15). A suspension of small pieces of sodium (235 mg, 10.2 mmol) and naphthalene (289 mg, 2.25 mmol) in THF (5 mL) was sonicated for 45 min at rt. The dark purple solution was transferred via cannula to a flask under Ar, and the excess sodium was washed with THF (3 mL). The vessel was cooled to –50 ºC and a solution of dimethyl naphthalene-1,4-dicarboxylate **11b** (250 mg, 1.02 mmol) in THF (1 mL) was added, stirred for 6 h, and treated with *t*-butyl iodide (135 μL, 1.13 mmol). The reaction mixture was slowly warmed to –30 ºC and stirred for 16 h, deoxygenated MeOH (105 μL, 2.56 mmol) was added and stirred for 3h at –30 ºC. Work-up as above gave a residue that was purified by flash column chromatography (15-42 μm SiO_2, 50-70% CH_2Cl_2/hexane) to give **15** (165 mg, 53%) as a colorless oil. ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.81 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.47 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.27 (td,

J = 7.6, 1.5 Hz, 1H), 7.22 (td, *J* = 7.6, 1.6 Hz, 1H), 6.99 (dd, *J* = 6.5, 3.2 Hz, 1H), 3.81 (s, 3H), 3.66 (s, 3H), 3.31 (dd, *J* = 18.9, 3.2 Hz, 1H), 2.85 (dd, *J* = 18.9, 6.6 Hz, 1H), 1.02 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, CD_2Cl_2) δ 175.5, 167.3, 138.8, 134.0, 131.6, 130.3, 130.1, 127.6, 127.5, 126.7, 56.4, 52.5, 52.2, 39.3, 30.3, 27.8; IR (neat): 1715 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{23}O_4$ 303.1591, found 303.1588.

Ring-Opening and Alkylation Reactions from Bicycle 16. A suspension of Li (36 mg, 5.18 mmol) and naphthalene (290 mg, 2.26 mmol) in THF (5 mL) was sonicated at room temperature for 45 min. The solution was transferred via cannula to another round-bottomed flask, washed with THF (5 mL), cooled to –30 ºC, and treated with a solution of **16** (300 mg, 1.02 mmol) in THF (1 mL). After 1 h, the reaction mixture was treated with *t*-butyl iodide (490 μL, 4.11 mmol). The reaction was stirred for an additional 20 h while slowly warming to rt, quenched with pH 7 buffer solution (20 mL) and extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried, filtered, and evaporated under reduced pressure. Purification by column chromatography (15-42 μm SiO_2, 50-70% CH_2Cl_2/Hexane) afforded **18a** (63 mg, 21%) and **19** (133 mg, 37%) as clear oils.

Isopropyl 6-(*t*-butyl)-10-oxobicyclo[4.3.1]deca-2,4-diene-1-carboxylate (18a). ^{1}H NMR (500 MHz, DMSO-D_6, 100 ºC) δ 5.93 (m, 2H), 5.85 (m, 1H), 5.61 (m, 1H), 4.98 (hept, *J* = 6.2 Hz, 1H), 2.34 (td, *J* = 12.9, 4.1 Hz, 1H), 2.00 (ddd, *J* = 13.3, 12.0, 4.4 Hz, 1H), 1.93-1.69 (m, 4H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.06 (s, 9H); $^{13}C\{^{1}H\}$ NMR (126 MHz, DMSO-D_6) δ 205.0, 170.2, 130.4, 128.1, 123.6, 122.9, 67.6, 65.9, 60.6, 36.0, 35.7, 34.0, 26.1, 20.9, 20.7, 17.0; IR (neat): 1733 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{27}O_3$ 291.1955, found 291.1957.

Diisopropyl 1-(*t*-butyl)-1,4,5,6,7,7a-hexahydro-3a*H*-indene-3a,7-dicarboxylate (19). Compound **19** was isolated as a 2:3 mixture of isomers in 37% combined yield. Minor

isomer (51 mg, 14%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (dd, *J* = 5.8, 2.6 Hz, 1H), 5.59 (dd, *J* = 5.8, 1.8 Hz, 1H), 4.98 (hept, *J* = 6.3 Hz, 1H), 4.90 (hept, *J* = 6.3 Hz, 1H), 2.91 (dd, *J* = 4.8, 2.9 Hz, 1H), 2.81 (dt, *J* = 13.0, 4.1 Hz, 1H), 2.56 (q, *J* = 2.5 Hz, 1H), 1.80 (m, 1H), 1.71-1.44 (m, 5H), 1.28-1.16 (m, 12H), 0.75 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.6, 175.1, 134.1, 133.1, 67.9, 67.7, 60.2, 56.8, 41.0, 40.6, 33.2, 27.7, 27.5, 22.2, 21.9, 21.8, 17.5, 15.8; IR (neat): 1718 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{21}H_{35}O_4$ 351.2530, found 351.2532.

Major isomer (82 mg, 23%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (dd, *J* = 5.8, 2.3 Hz, 1H), 5.59 (dd, *J* = 5.8, 1.9 Hz, 1H), 4.97 (dhept, *J* = 8.6, 6.2 Hz, 2H), 2.97 (dd, *J* = 6.2, 4.8 Hz, 1H), 2.42 (q, *J* = 6.2 Hz, 1H), 2.29 (dt, *J* = 4.5, 2.1 Hz, 1H), 1.87 (m, 2H), 1.63 (m, 2H), 1.44 (m, 2H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.20 (dd, *J* = 6.2, 1.4 Hz, 6H), 0.86 (s, 9H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 176.0, 175.5, 134.8, 132.4, 67.7, 67.7, 62.4, 58.5, 44.1, 41.5, 33.6, 30.6, 28.1, 22.8, 22.0, 21.9, 21.9, 21.8, 17.4; IR (neat): 1711 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{21}H_{35}O_4$ 351.2530, found 351.2532.

Isopropyl 6-isopropyl-10-oxobicyclo[4.3.1]deca-2,4-diene-1-carboxylate (18b). Following the same procedure as for **18a**, starting from **16** (143 mg, 0.49 mmol) and using 2-bromopropane as the electrophile (182 μL, 1.94 mmol), **18b** was isolated as a colorless oil in 74% yield (100 mg) after column chromatography purification (SiO_2, 2-5% EtOAc/Hex). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96-5.78 (m, 3H), 5.38 (d, *J* = 11.6 Hz, 1H), 5.08 (hept, *J* = 6.3 Hz, 1H), 2.40 (m, 1H), 2.15 (quint, *J* = 6.9 Hz, 1H), 1.99-1.83 (m, 3H), 1.82-1.66 (m, 2H), 1.25 (dd, *J* = 6.5, 2.8 Hz, 6H), 0.94 (t, *J* = 6.5 Hz, 6H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 206.1, 171.6, 131.7, 128.2, 124.6, 123.9, 69.0, 66.4, 59.3, 37.5, 35.7, 32.8, 21.8, 21.6, 18.5, 17.9; IR (neat): 1711 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{25}O_3$ 277.1798, found 277.1799.

Diisopropyl 5-(adamantan-1-yl)-2,3-dihydro-1*H*-indene-3a,7a-dicarboxylate (24). A –78 ºC suspension of small pieces of sodium (245 mg, 10.6 mmol) and naphthalene (150 mg, 1.17 mmol) in THF (4 mL) was treated with a solution of **1** (250 μL, 1.06 mmol) in THF (1 mL) and stirred for 6 h. The resulting solution was transferred via cannula to a –78 ºC flask, washed with THF (5 mL) and treated with a solution of 1-iodoadamantane (305 mg, 1.17 mmol) in DMF (1 mL). The reaction mixture was slowly warmed to –30 ºC and stirred for 16 h, treated with 1,3-dibromopropane (120 μL, 1.17 mmol) and stirred for 8 h at rt. The reaction mixture was cooled to 0 ºC, DBU (175 μL, 1.17 mmol) was added, and stirring was continued for an additional 16 h at rt. The reaction mixture was partitioned between EtOAc (10 mL) and pH 7 buffer solution (10 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layer was washed with 10% aqueous $Na_2S_2O_3$ solution (10 mL) and brine (10 mL), dried, filtered and evaporated. The residue was purified by flash column chromatography (SiO_2, 2-5% EtOAc/hexane) to yield **24** as a pale yellow oil (261 mg, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (d, J = 10.0 Hz, 1H), 5.91 (d, J = 9.9 Hz, 1H), 5.40 (s, 1H), 4.93 (hept, J = 6.3 Hz, 2H), 2.48 (m, 1H), 2.38 (ddd, J = 13.9, 9.2, 5.4 Hz, 1H), 2.04-1.89 (m, 5H), 1.77-1.48 (m, 14H), 1.17 (m, 12H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 174.1, 174.0, 141.7, 130.4, 121.8, 121.1, 67.8, 67.7, 56.5, 55.6, 40.7, 40.1, 39.9, 37.0, 35.5, 28.6, 21.8, 21.7, 21.7, 21.3; IR (neat): 1722 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{27}H_{39}O_4$ 427.2843, found 427.2840.

Synthesis of Diol 25. A solution of **24** (60 mg, 0.14 mmol) in THF (1 mL) was slowly added to a 0 ºC suspension of $LiAlH_4$ (12.5 mg, 0.31 mmol, 95%) in THF (1 mL). The reaction mixture was stirred at room temperature for 3 h. After cooling to 0 ºC, EtOAc (0.5 mL) was slowly added, followed by $CHCl_3$ (2 mL), sat. Na_2CO_3 (1 mL), KH_2PO_4, and Na_2SO_4. The resulting mixture was stirred at room temperature for 1 h, filtered over celite, and washed with $CHCl_3$ (10 mL). The combined clear filtrate and washings were evaporated

to give a colorless residue. Column chromatography purification (SiO_2, 20% EtOAc/Hex) afforded **25** as a white solid (40.3 mg, 91%). Mp 140-141 ºC (EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.12 (d, *J* = 9.9 Hz, 1H), 5.53 (d, *J* = 9.9 Hz, 1H), 5.10 (s, 1H), 3.69 (d, *J* = 11.5 Hz, 2H), 3.44 (dd, *J* = 11.6, 6.2 Hz, 2H), 3.23 (br s, 1H), 3.04 (br s, 1H), 2.01 (s, 3H), 1.82-1.50 (m, 17H), 1.44 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 143.8, 133.8, 124.2, 123.0, 67.1, 66.7, 50.3, 50.1, 40.9, 38.3, 37.9, 37.0, 35.5, 28.6, 21.8; HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{21}H_{31}O_2$ 315.2319, found 315.2318.

General Procedure C for the Synthesis of Spirocycles 28. A –78 ºC suspension of small pieces of sodium (245 mg, 10.65 mmol) and naphthalene (150 mg, 1.17 mmol) in THF (4 mL) was treated with a solution of **1** (250 μL, 1.06 mmol) in THF (1 mL) and stirred for 6 h. The resulting solution was transferred via cannula to a –78 ºC flask, and treated with 1-iodopropane (109 μL, 1.12 mmol). The reaction mixture was stirred for 16 h at -78 ºC, quenched by addition of deoxygenated HOAc (150 μL, 2.6 mmol) and then partitioned between EtOAc (10 mL) and pH 7 phosphate buffer (10 mL). The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic extracts were washed with aqueous saturated $Na_2S_2O_3$ (10 mL) and brine (10 mL), dried and concentrated. The residue was purified by flash column chromatography (SiO_2, 2-5% EtOAc/hexane) to yield **27** (250 mg, 80%) as a colorless oil.

A –30 ºC suspension of NaH (40 mg, 1.69 mmol) and *i*PrOH (catalytic amount) in THF (9 mL) was treated with a solution of **27** (100 mg, 0.34 mmol) in THF (1 mL). The reaction mixture was stirred for 2 h at –30 ºC, then cooled down to –78 ºC and the corresponding *bis*-electrophile was added (0.39 mmol). The reaction mixture was stirred for 20 h while slowly warming to rt, then quenched by addition of a solution of HOAc (1 mL) in H_2O (5 mL), and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with H_2O (2 x 10 mL) and brine (10 mL), dried (anhydrous Na_2SO_4), filtered and

concentrated to a residue that was purified by column chromatography (SiO_2, 9% EtOAc:Hexane).

Diisopropyl 8-propylspiro[4.5]deca-6,9-diene-7,8-dicarboxylate (28a). Following general procedure C, and using 1,4-dibromobutane (45 μL, 0.39 mmol) as the electrophile, **28a** was isolated as a colorless oil (105 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.93 (d, *J* = 2.0 Hz, 1H), 5.69 (dd, *J* = 9.8, 2.0 Hz, 1H), 5.29 (d, *J* = 9.9 Hz, 1H), 5.05 (hept, *J* = 6.3 Hz, 1H), 4.93 (hept, *J* = 6.3 Hz, 1H), 2.16 (m, 1H), 1.88-1.50 (m, 9H), 1.25 (dd, *J* = 9.7, 6.3 Hz, 6H), 1.16 (d, *J* = 6.3 Hz, 6H), 1.07 (m, 1H), 0.86 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.6, 166.1, 146.5, 133.9, 127.5, 126.0, 68.0, 68.0, 50.2, 45.3, 41.2, 40.8, 37.0, 25.0, 24.9, 21.9, 21.7, 21.7, 18.0, 14.5; IR (KBr): 1732 cm^{-1} (C=O); HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{21}H_{33}O_4$ 349.2373, found 349.2376; Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.67; H, 9.03.

Diisopropyl 3-propylspiro[5.5]undeca-1,4-diene-2,3-dicarboxylate (28b). Following general procedure C, and using 1,5-dibromopentane (50 μL, 0.39 mmol) as the electrophile, **28b** was isolated as a colorless oil (107 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (d, *J* = 1.9 Hz, 1H), 5.88 (dd, *J* = 10.1, 2.0 Hz, 1H), 5.32 (d, *J* = 10.0 Hz, 1H), 5.06 (hept, *J* = 6.2 Hz, 1H), 4.93 (hept, *J* = 6.2 Hz, 1H), 2.15 (td, *J* = 13.4, 4.1 Hz, 1H), 1.72 (m, 1H), 1.65-1.35 (m, 10H), 1.25 (dd, *J* = 9.6, 6.3 Hz, 6H), 1.16 (d, *J* = 6.2 Hz, 6H), 1.07 (m, 1H), 0.86 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.5, 166.1, 146.5, 133.4, 128.1, 126.9, 68.0, 50.9, 38.1, 37.7, 37.5, 36.9, 31.7, 26.0, 22.8, 21.9, 21.7, 21.7, 21.3, 18.3, 14.5, 14.3; IR (KBr): 1732 cm^{-1} (C=O); HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{22}H_{35}O_4$ 363.2530, found 363.2527; Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.07; H, 9.77.

Diisopropyl 4-propyl-5',7'-dihydrospiro[cyclohexane-1,6'-dibenzo[*a*,*c*][7]annulene]-2,5-diene-3,4-dicarboxylate (28c). Following general procedure C, and using 2,2'-*bis*(cloromethyl)-1,1'-biphenyl (100 mg, 0.39 mmol) as the electrophile,

28c was isolated as a colorless oil (107 mg, 67%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.46 (m, 2H), 7.41 (td, *J* = 7.5, 1.3 Hz, 2H), 7.34 (tt, *J* = 7.6, 2.2 Hz, 2H), 7.23 (dd, *J* = 13.2, 7.4 Hz, 2H), 6.99 (d, *J* = 2.0 Hz, 1H), 5.82 (dd, *J* = 9.9, 2.0 Hz, 1H), 5.42 (d, *J* = 9.9 Hz, 1H), 5.04 (hept, *J* = 6.2 Hz, 1H), 4.93 (hept, *J* = 6.3 Hz, 1H), 2.45 (br s, 4H), 2.19 (td, *J* = 13.1, 4.2 Hz, 1H), 1.78 (td, *J* = 13.4, 4.3 Hz, 1H), 1.31-1.09 (m, 13H), 0.97 (m, 1H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.1, 165.9, 144.3, 141.0, 140.9, 135.7, 132.6, 130.0, 129.9, 129.0, 128.5, 128.4, 127.7, 127.5, 127.4, 68.2, 50.9, 49.1, 44.1, 43.7, 36.9, 21.9, 21.8, 21.7, 18.3, 14.6; IR (KBr): 1730 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{31}H_{37}O_4$ 473.2686, found 473.2687.

Diisopropyl 4-propyl-1',3'-dihydrospiro[cyclohexane-1,2'-indene]-2,5-diene-3,4-dicarboxylate (28d). Following general procedure C, and using *o*-dichloroxylene (70 mg, 0.39 mmol) as the electrophile, **28d** was isolated as a colorless oil (122 mg, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (m, 4H), 7.04 (d, *J* = 2.1 Hz, 1H), 5.84 (dd, *J* = 9.9, 2.0 Hz, 1H), 5.39 (d, *J* = 9.8 Hz, 1H), 5.05 (hept, *J* = 6.3 Hz, 1H), 4.96 (hept, *J* = 6.2 Hz, 1H), 3.00 (m, 4H), 2.20 (ddd, *J* = 13.8, 12.0, 4.0 Hz, 1H), 1.77 (m, 1H), 1.25 (d, *J* = 6.2 Hz, 3H), 1.23 (d, *J* = 6.2 Hz, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.12 (m, 1H), 0.98-0.84 (m, 4H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 173.3, 165.9, 145.0, 141.4, 141.3, 133.0, 128.8, 127.3, 126.9, 126.9, 124.8, 124.8, 68.2, 68.2, 50.4, 47.1, 46.8, 46.1, 36.9, 21.9, 21.8, 21.7, 18.1, 14.5; IR (KBr): 1730 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for for $C_{25}H_{33}O_4$ 397.2373, found 397.2369. Anal. Calcd for $C_{25}H_{32}O_4$: C, 75.73; H, 8.13. Found: C, 75.39; H, 8.51.

Diisopropyl 4-propyl-1'*H*,3'*H*-spiro[cyclohexane-1,2'-phenalene]-2,5-diene-3,4-dicarboxylate (28e). Following general procedure C, and using 1,8-*bis*-(chloromethyl)naphthalene (90 mg, 0.39 mmol) as the electrophile, **28e** was isolated as a colorless oil (133 mg, 88%). ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.73 (dt, *J* = 8.5, 1.5 Hz, 2H),

7.42 (ddd, J = 8.2, 7.0, 4.3 Hz, 2H), 7. 24 (ddd, J = 13.1, 7.0, 1.2 Hz, 2H), 6.88 (d, J = 2.1 Hz, 1H), 5.61 (dd, J = 10.0, 2.1 Hz, 1H), 5.37 (d, J = 10.0 Hz, 1H), 5.01 (hept, J = 6.2 Hz, 1H), 4.93 (hept, J = 6.2 Hz, 1H), 3.22 (dd, J = 15.8, 4.0 Hz, 2H), 3.05 (t, J = 15.6 Hz, 2H), 2.18 (ddd, J = 13.7, 12.5, 4.7 Hz, 1H), 1.75 (ddd, J = 13.7, 12.3, 4.4 Hz, 1H), 1.26-1.13 (m, 13H), 0.98 (m, 1H), 0.91 (t, J = 7.1 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (75 MHz, $CDCl_3$) δ 173.1, 165.9, 145.0, 133.3, 132.4, 132.2, 131.7, 129.9, 129.2, 128.3, 126.6, 126.5, 125.9, 125.3, 125.2, 68.3, 68.3, 50.9, 43.0, 42.6, 37.6, 36.9, 21.9, 21.9, 21.8, 21.8, 18.3, 14.5; IR (KBr): 1730 cm^{-1} (C=O); HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{29}H_{35}O_4$ 447.2530, found 447.2524.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. ^{1}H NMR spectra of *bis*-enolate **2** (with sodium and lithium counterions), EPR spectra of sodium *bis*-enolate **2** (containing Na/naphthalene) and Na/naphthalene, ^{1}H NMR of monoenolate **22** obtained by quenching *bis*-enolate **2** with excess adamantyl iodide and ^{1}H NMR of monoenolate **29** obtained by quenching *bis*-enolate **2** with excess isopropyl bromide, X-ray crystallographic data and ORTEP of **5a**, **6**, **10**, and **25**; ^{1}H and ^{13}C NMR spectra for all new compounds.

Acknowledgements

Financial support from Ministerio de Economía y Competitividad of Spain (CTQ2017-84354-P), Xunta de Galicia (GRC 2014/029 and Centro singular de investigación de Galicia accreditation 2016-2019, ED431G/09) and the European Union (European Regional Development Fund-ERDF) is gratefully acknowledged.

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