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Enantioselective Annulation Reactions of *Bis*-enolates Prepared through Dearomatization Reactions of Aromatic and Heteroaromatic Diesters

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A one-pot, enantioselective strategy for the dearomatization-annulation of aromatic diesters to give a range of highly functionalized polycyclic molecules with excellent enantioselectivities is presented. This methodology is based on the reaction of *bis*-enolates, prepared by treating aromatic diesters with trialkyltin lithium reagents, a process which involves a stanna-Brook rearrangement, with 1,ω-dihaloalkanes and other *bis*-electrophiles. We have also developed experimental conditions for performing these reactions with substoichiometric amounts of the required tin reagent, by in situ recycling Me_6Sn_2 into Me_3SnLi with excess lithium metal, and provide a study of the scope and limitations of this synthetic methodology.

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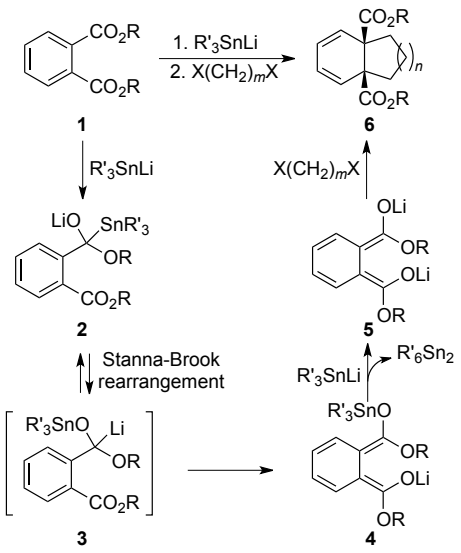
Introduction

Synthetic methodologies based on the use of tandem dearomatization[1]-alkylation reactions hold great potential for the preparation of complex organic structures.[2] Several of the general methods available to dearomatize arene compounds, such as nucleophilic addition to aromatic rings,[1a,3] oxidation,[4] reduction,[5] and transition-metal-mediated processes[6] (along with some other reactions of narrower scope[7]) have been developed into highly useful tandem dearomatization-alkylation protocols. To further increase the synthetic value of this type of approaches, several enantioselective variants of some of these transformations have been developed.[2,4] Worthy of note in this particular respect are the alkylative-dearomatization reactions of phenols[2d-e] and anilines.[2f]

Despite of their great potential, there is a certain scarcity of synthetic tandem procedures based on *reductive* dearomatization reactions coupled to alkylative processes. This is surprising considering that these reductive dearomatizations provide an efficient route to highly nucleophilic anionic, or even dianionic, intermediates that could be advantageously used for C-C bond formation (for instance, for the stereocontrolled construction of quaternary stereocenters[8]). One could even envision the coupling of a reductive dearomatization process and an annulation reaction to open short routes for the preparation of complex cyclic frameworks present in natural and bioactive compounds. Notwithstanding these attractive possibilities, there have only appeared a handful of publications describing useful results in this area.[9]



Scheme 1. Mechanism for the Dearomatization-Alkylation Procedure Mediated by Me_3SnLi.

In the past few years we have undertaken a program to broaden the synthetic utility of dearomatization reactions by coupling them to annulation protocols. In this area, we have reported the successful pairing of a novel dearomatization reaction of phthalates and related diesters, brought about by anionic tin nucleophiles, with a *bis*-alkylation reaction. This tandem sequence allows the stereoselective preparation of 6,5-, 6,6- and 6,7-fused carbobicyclic and heterobicyclic systems, with the concomitant formation of one or two quaternary stereocenters in the process.[10] Our procedure involves the treatment of benzene and pyridine diesters with R_3SnLi, to provide highly nucleophilic *bis*-enolates (a process in which a stanna-Brook rearrangement[11] is involved) followed by trapping the intermediates with 1,ω-dihaloalkanes and related *bis*-electrophiles. This dearomatization-alkylation procedure (Scheme 1) does not result from the nucleophilic addition of trialkylstannyllithium to the electron-deficient aromatic ring (as in

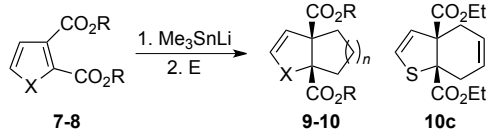
many nucleophilic addition-initiated dearomatization reactions),[1a,3] but instead from 1,2-addition to a carboxylate group, followed by 1,2 Li-Sn rearrangement of the initial stannyl alkoxide adduct (Scheme 1). Reaction of **4** with a second equivalent of R_3SnLi gives rise to the *bis*-enolate **5**, which is finally trapped with different *bis*-electrophiles to yield the observed bicyclic products.

Herein we report the results of our work aimed at increasing the usefulness and applicability of this methodology. Firstly we explored the scope of the reaction with regards to the type of aromatic diesters that could be used (for example, five-membered ring heteroaromatics, such as furan, thiophene, benzofuran, as well as naphthalene-derivatives). Secondly we undertook the task of finding reaction conditions that would require only substoichiometric (catalytic) amounts of tin reagents (due to their toxicity and expensive nature). Finally we engaged in the development of an enantioselective variant of this transformation.

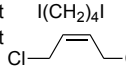
Results and Discussion

We first studied the behaviour of 5-membered-ring aromatic heterocycles, such as furan and thiophene. Dearomatized furans[12] have been previously obtained by decarboxylative Claisen rearrangement,[7b] [2,3]-Still-Wittig rearrangement,[13] aryl radical addition[14] or nucleophilic addition to carbene complexes of chromium,[15] among other methods.[16]

Furan diester **7** (X = O) was prepared by Fischer esterification in *i*PrOH of the corresponding diacid, which in turn was obtained by regioselective deprotonation at C-2 of 3-furoic acid with BuLi followed by quenching with carbon dioxide.[17] Treatment of a THF solution of **7** with Me_3SnLi (215 mol-%) at low temperature, followed by trapping of the intermediate *bis*-enolate with 1,3-diiodopropane (120 mol-%) afforded the 5,5-fused bicyclic compound **9a**. The ^{1}H NMR of the crude reaction mixture showed dearomatized **9a** as the main product, together with minor proportions of starting material, a ring-opened product, and the monoacid derived from partial hydrolysis of **7**.[18] After chromatographic purification, **9a** was isolated in 63% yield. When 1,4-diiodobutane was used as the electrophile under the same reaction conditions, **9b** was obtained in 59% yield. The ring-forming *bis*-alkylation of the furan-derived *bis*-enolate proved to be more difficult with 1,5-diiodopentane but, as observed previously with phthalate and pyridine diesters,[10] the 5,7-fused bicycle **9c** could also be prepared, albeit in a lower yield (48%), by warming up the reaction mixture to 40 °C. All bicyclic compounds were obtained with complete stereoselectivity, as only one stereoisomer was detected in the ^{1}H NMR spectra of the crude reaction mixtures.



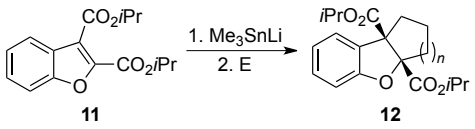
7-8 **9-10** **10c**

Entry	**7-8**	X	R	E	Product	*n*	Yield (%)
1	**7**	O	*i*Pr	$I(CH_2)_3I$	**9a**	1	63
2	**7**	O	*i*Pr	$I(CH_2)_4I$	**9b**	2	59
3	**7**	O	*i*Pr	$I(CH_2)_5I$	**9c**	3	48
4	**8**	S	Et	$I(CH_2)_3I$	**10a**	1	55
5	**8**	S	Et	$I(CH_2)_4I$	**10b**	2	60
6	**8**	S	Et		**10c**	-	52

Scheme 2. Dearomatizing Anionic Cyclization of Furan and Thiophene Diesters.

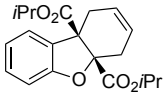
Diethyl thiophene-2,3-dicarboxylate (**8**, X = S) was obtained by Fischer esterification of the corresponding diacid, which in turn was prepared by dilithiation of thiophene 2-carboxylic acid with BuLi followed by quenching with carbon dioxide.[19] In a manner analogous to that of furan **7**, when the dearomatization-*bis*-alkylation procedure was applied to **8**, fused 5,5-, and 5,6-ring systems were obtained after sequential treatment with Me_3SnLi and 1,3-diiodopropane (**10a**, 55%) or 1,4-diiodobutane (**10b**, 60%). Again some starting material and a ring-opened product were observed in the reaction mixture. When a functionalized *bis*-electrophile, such as *cis*-1,4-dichloro-2-butene, was used the expected tetrahydrobenzothiophene **10c** was isolated in 52% yield.

We then investigated the behaviour of benzofuran diester **11**. Benzofurans have been used recently in dearomatizing [4+2] cycloadditions,[7a] and radical reactions.[20] Under stanna-Brook conditions, benzofuran **11** was transformed into the corresponding *bis*-enolate that was alkylated with different 1,ω-dihaloalkanes to give the corresponding tricyclic compound **12** (n = 1-3) in good yields (see Scheme 3).



11 **12**

Entry	E	Product	*n*	Yield (%)
1	$I(CH_2)_3I$	**12a**	1	70
2	$I(CH_2)_4I$	**12b**	2	68
3	$I(CH_2)_5I$	**12c**	3	59
4		**12d**	-	60

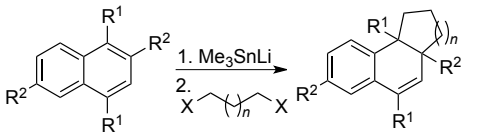


12d

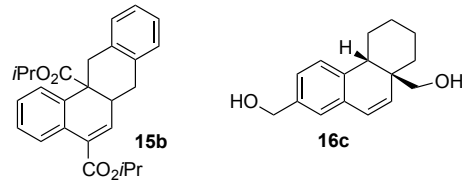
Scheme 3. Dearomatizing Anionic Cyclizations of Benzofuran Diesters.

Naphthalene-diester derivatives, with different patterns of substitution, were also investigated as substrates for our dearomatization-annulation methodology. We first explored the behaviour of naphthalene systems possessing the two required carboxylate moieties in the same ring. Unfortunately, under the reaction conditions employed, 1,2- and 2,3-disubstituted naphthalenes afforded complex reaction mixtures. The results obtained with 1,2-disubstituted naphthalene may be due to the instability of the intermediate *bis*-enolate to form, due to the steric crowding around the substituent in position 1. The total loss of the aromaticity of both rings in the intermediate *bis*-enolate derived from the 2,3-disubstituted naphthalene diester can account for the observed results in this particular case. In stark contrast with these negative results, reaction of diisopropyl naphthalene-1,4-dicarboxylate (**13**) with Me_3SnLi followed by addition of 1,3-dibromopropane provided tricyclic compound **15a** in an 87% isolated yield. The analogous reaction using 1,4-diiodobutane as the *bis*-electrophile did not provide the desired tricyclic diester, but instead a mixture of mono- and dialkylated compounds. The use of a more rigid *bis*-electropile, such as 1,2-bis(chloromethyl)benzene, proved more successful and allowed the preparation of the

tetracyclic product **15b** in 60% yield. However, with 1,4-dichloro-2-butene no alkylation was observed and starting ester **13** was recovered. This unexpected result is probably due to the fact that the electrophile acts as a chlorinating agent with concomitant liberation of butadiene, and not as a C-electrophile.



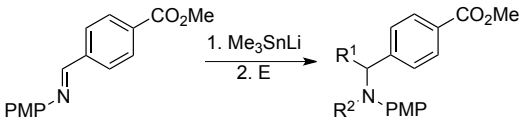
Entry	13-14	R^1	R^2	X	Product	*n*	Yield
1	**13**	CO_2*i*Pr	H	Br	**15a**	1	87%
2	**13**	CO_2*i*Pr	H	-	**15b**	-	60%
3	**14**	H	CO_2*i*Pr	Br	**16a**	1	79%
4	**14**	H	CO_2*i*Pr	I	**16b**	2	66%



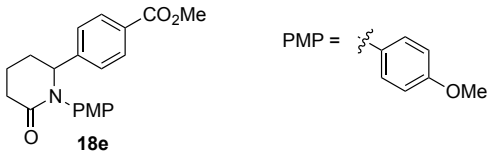
Scheme 4. Dearomatizing Anionic Cyclizations of Naphthalene Derivatives.

We then proceeded to study the behaviour of naphthalene systems where the required carboxylates were attached to different rings. Complex mixtures were obtained for the reaction of 1,5-naphthalene dicarboxylate with Me_3SnLi and 1,ω-dihaloalkanes, but when diisopropyl naphthalene-2,6-dicarboxylate (**14**) was treated with Me_3SnLi followed by the addition of 1,3-dibromopropane or 1,4-diiodobutane, the desired cyclized products **16a** and **16b** were isolated in 79 and 66% yield, respectively. The *syn*-fusion of the new ring was confirmed by X-ray crystallographic analysis of the diol **16c**, obtained by $LiAlH_4$ reduction of **16b** in THF at 0 °C.[21]

We next decided to explore whether the presence of *two* carboxylate groups in the aromatic system was an absolute requirement for the dearomatization reaction to take place. In principle, the stanna-Brook reaction could also take place if one of the carboxylate groups were replaced by a different electron-withdrawing group. To explore this hypothesis we studied the behaviour of several benzoates further substituted in their *p*- and *o*-positions with different electron-withdrawing groups. Complex reaction mixtures were obtained when keto, formyl, nitro or cyano benzoates[22] were used as substrates, but *p*-imino substituted benzoates, bearing a PMP moiety as the *N*-protecting group, were found to provide clean reactions when submitted to the stanna-Brook-*bis*-alkylation protocol. Interestingly, we did not detect dearomatized products after treatment of *p*-imino-benzoate **17** with Me_3SnLi followed by the addition of an electrophile, instead we observed that the *bis*-alkylation took place on the N and C atoms originally forming the imine group, and that the regioselectivity of the process could be easily controlled. Thus, treatment of **17** with Me_3SnLi in THF at low temperature followed by addition of 1-iodopropane, afforded the C-alkylated, secondary benzylamine **18a** in 78% yield. The alkylation reaction was shown to be regioselective as it proceeded exclusively on the imine carbon. However, the use of a harder electrophile, such as Me_2SO_4, gave mainly the *N*-methylated, C-unsubstituted product **18b**. Additionally, the use of *bis*-electrophiles such as 1,3-dibromopropane or 1,4-diiodobutane led to the corresponding pyrrolidine **18c** or piperidine **18d** in good yields. δ-Lactam **18e** was also easily prepared in good yield when methyl γ-iodobutyrate was used as the *bis*-electrophile.

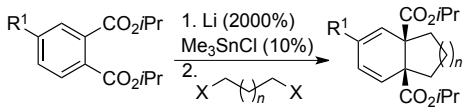


Entry	Product	E	R^1	R^2	Yield (%)
1	**18a**	$I(CH_2)_2CH_3$	Pr	H	78
2	**18b**	Me_2SO_4	H	Me	60
3	**18c**	$Br(CH_2)_3Br$	$(CH_2)_3$		87
4	**18d**	$I(CH_2)_4I$	$(CH_2)_4$		75
5	**18e**	$I(CH_2)_3CO_2Me$	$(CH_2)_3CO$		67



Scheme 5. Me_3SnLi Addition to *p*-Imino Benzoate **17**.

In all the annulations described so far, the required Me_3SnLi was prepared by treatment of a THF solution of hexamethyldistannane with MeLi[23] because of the simplicity of the procedure and the homogeneity of the reaction mixture obtained, although in this process one equivalent of tin is wasted as Me_4Sn. An alternative procedure for the preparation of Me_3SnLi involves the reaction of Me_6Sn_2 or Me_3SnCl with excess lithium in THF.[24] Since, according to our proposed mechanism for the stanna-Brook rearrangement, a molecule of Me_6Sn_2 is obtained per *bis*-enolate molecule formed, we decide to explore if this di-tin compound could be recycled into Me_3SnLi in situ, thus turning the procedure catalytic in the tin reagent. To test this hypothesis, we prepared a solution of substoichiometric amount of Me_3SnLi from Me_3SnCl (10 mol-%) and excess lithium in THF at room temperature for 30 min. After cooling to -78 °C, a solution of diisopropyl phthalate (100 mol-%) in THF was added and the resulting mixture was stirred while a dark red color developed. Addition of 1,3-dibromopropane to this dark red solution provided the hydrindane **21a**, thus proving that Me_6Sn_2 could be successfully recycled into Me_3SnLi under the reaction conditions used. After some experimentation we discovered that the *bis*-enolate can be prepared after 16 h at -78 °C by using 2000 mol-% of lithium and 10 mol-% of Me_3SnCl. Under these conditions we have prepared the hydrindanes **21a** and **22a** in 77% and 60% yield, respectively (see Scheme 6). The hexahydronaphthalene **21b** was isolated in 68% yield when 1,4-diiodobutane was used as electrophile. This substoichiometric procedure can also be successfully applied to heteroaromatic diesters, as thiophene **8** (X = S) provided the expected bicycle **10b** in 56% yield. Despite the fact that the yields obtained using this catalytic procedure are slightly lower than when stoichiometric Me_3SnLi is used,[10] we consider that the economic savings and the lower toxicity of the process make it a valuable alternative. Some limitations to the general applicability of this catalytic procedure were found nevertheless, since no reaction was observed when terephthalate and naphthalene diesters were subjected to these conditions.

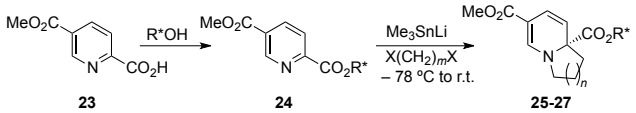


19-20 **21-22**

Entry	Diester	R^1	X	Product	*n*	Yield (%)
1	**19**	H	Br	**21a**	1	77
2	**19**	H	I	**21b**	2	68
3	**20**	Me	I	**22a**	1	60
4	**8**	-	I	**10b**	-	56

Scheme 6. Results Using Substoichiometric Sn-reagent.

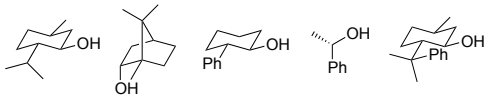
The next step in our exploration of this chemistry was the development of an asymmetric version of this methodology. Our entry to the asymmetric construction of quaternary centers relies on the use of esters derived from chiral alcohol auxiliaries. Thus we explored the behaviour of chiral *bis*-enolates in which all stereochemical information resides in the alcoholic component of the ester functionality. In particular, we chose for these preliminary assays the hindered esters derived from picolinic acid **23** and the following alcohols: (-)-menthol, (-)-borneol, (1*R*,2*S*)-*trans*-2-phenyl-1-cyclohexanol, (*S*)-1-phenylethanol and (-)-8-phenylmenthol. All esters were prepared using EDC as the coupling agent and DMAP as the nucleophilic catalyst in CH_2Cl_2. Sequential treatment of esters **24** with Me_3SnLi, to generate the chiral *bis*-enolate, followed by addition of 1,3-dibromopropane for the alkylation-cyclization process, afforded tetrahydroindolizines **25** in good unoptimized yields. As shown in Scheme 7, the best diastereomeric ratio (99:1) was obtained using (-)-8-phenylmenthol as chiral auxiliary (**25e**). A favorable face-to-face π-π interaction can explain the high degree of stereocontrol obtained in the alkylation of the *bis*-enolate (with the pending 8-phenylmenthyl moiety[25]) with 1,3-dibromopropane. Furthermore, when 1,4-dibromobutane and 1,5-diiodopentane were used as electrophiles, the corresponding quinolizine **26e** and azepine **27e** were also obtained with good diastereoselectivities (94:6 and 93:7, respectively). Single crystals of **25e** suitable for X-ray analysis were obtained by recrystallization from Et_2O/CH_2Cl_2. The X-ray analysis revealed that the absolute configuration of indolizine **25e** was *R*.[21]



23 **24** **25-27**

R*OH	**24**	Yield	Electrophile	Product	*n*	Yield	*dr*
(-)-menthol, **a**	**24a**	60%	$Br(CH_2)_3Br$	**25a**	1	58%	50:50
(-)-borneol, **b**	**24b**	66%	$Br(CH_2)_3Br$	**25b**	1	73%	60:40
(1*R*, 2*S*)-2-phenylcyclohexanol, **c**	**24c**	87%	$Br(CH_2)_3Br$	**25c**	1	88%	67:33
(*S*)-1-phenylethanol, **d**	**24d**	70%	$Br(CH_2)_3Br$	**25d**	1	71%	87:23
(-)-8-phenylmenthol, **e**	**24e**	81%	$Br(CH_2)_3Br$	**25e**	1	79%	99:1
(-)-8-phenylmenthol, **e**	**24e**		$Br(CH_2)_4Br$	**26e**	2	58%	94:6
(-)-8-phenylmenthol, **e**	**24e**		$I(CH_2)_5I$	**27e**	3	62%	93:7

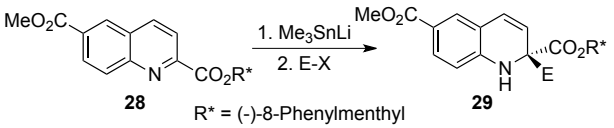
R*OH: **a** **b** **c** **d** **e**



Scheme 7. Asymmetric Dearomatization-Cyclization of Pyridine Diesters.

Once we had shown the successful enantioselective dearomatization-annulation process in pyridine diesters, we chose a different heteroaromatic system to prove the enantioselective dearomatization-alkylation with more elaborated nucleophiles and electrophiles. Thus when quinoline diester **28** was treated with Me_3SnLi, followed by the addition of primary halides (Scheme 8), the expected products were obtained with excellent enantioselectivity and fair to excellent chemical yields.

A limitation of this enantioselective dearomatizing annulation was found when our attempts to carry out the reactions using substoichiometric amounts of tin compounds failed. Complex reaction mixtures were obtained from these experiments. We believe that the slow formation of the required *bis*-enolates under the substoichiometric conditions allows ample opportunity for decomposition reactions to take place, probably caused by the bulkiness of the chiral auxiliary.

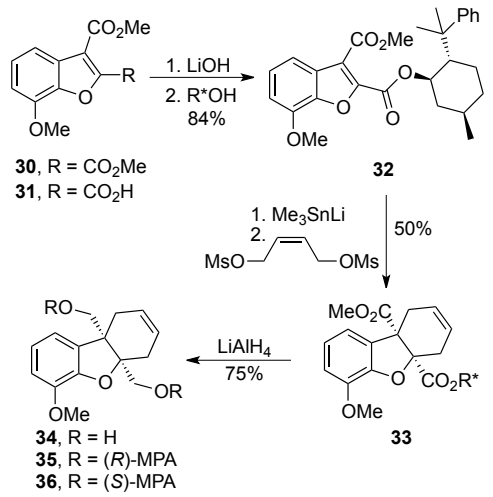


28 R* = (-)-8-Phenylmenthyl **29**

E-X	Product	Yield	*dr*
Pr-I	**29a**	90%	98:2
Br	**29b**	77%	96:4
Ph, Br	**29c**	70%	97:3
O, O, Br	**29d**	48%	95:5

Scheme 8. Asymmetric Dearomatization-Alkylation of Quinoline Diester.

As a synthetic application of this methodology, we developed an enantioselective approach to the tricyclic benzofuran derivative **33**, a projected intermediate for the synthesis of analogs of galantamine,[26] an alkaloid that acts as a selective, reversible, and competitive acetylcholinesterase inhibitor. 7-Methoxybenzofuran **30** was prepared from commercially available 2-methoxyphenol in three steps[27] in 41% overall yield. Selective hydrolysis of the ester in the 2-position was quantitatively achieved by using LiOH in a 1:1 dioxane:H_2O mixture. Esterification of **31** with (-)-8-phenylmenthol in the presence of EDC and DMAP in CH_2Cl_2, afforded chiral diester **32** in 84% yield. Treatment of **32** with Me_3SnLi to give a chiral *bis*-enolate, followed by alkylation with *cis*-2-butene-1,4-diol dimesylate led to the tricycle **33** in 50% yield. Careful examination of the ^1H NMR of the crude reaction mixture showed that the reaction took place with very high diastereoselectivity as only one diasteroisomer could be identified. To confirm the level of diastereoselection, the tricyclic compound was reduced to the diol **34** with $LiAlH_4$ in 75% yield and then the derived esters from **34** and both enantiomers of α-methoxyphenylacetic (MPA) acid[28] were prepared. 500 MHz ^1H NMR spectroscopy analyses of the crude mixtures showed an enantiomeric ratio of 98:2, proving again that (-)-8-phenylmenthol is an excellent chiral inductor for the *bis*-alkylation of lithium *bis*-enolates obtained from the stanna-Brook rearrangement of heteroaromatic diesters.



Scheme 9. Asymmetric Dearomatization-Cyclization of Benzofuran **30**.

Conclusions

In summary, we have developed a one-pot, enantioselective strategy for the dearomatization-annulation of aromatic diesters to give a range of highly functionalized polycyclic molecules with excellent enantioselectivities. For some compounds we have found experimental conditions for performing the reaction with substoichiometric amounts of the required tin reagent. Currently, we are investigating the application of this process to the synthesis of natural products.

Experimental Section

Diisopropyl furan-2,3-dicarboxylate (7). A solution of furan-2,3-dicarboxylic acid[17] (625 mg, 4.0 mmol) in toluene (40 mL) and *i*PrOH (20 mL) was treated with H_2SO_4 (130 μL) and refluxed using a Dean-Stark trap. During the first 6 h, 6 mL of distillate were withdrawn every hour and replenished by an equal volume of 2:1 toluene-*i*PrOH mixture. After 24 h, the solution was cooled to room temperature and concentrated in vacuo to 5 mL, diluted with CH_2Cl_2, and washed with cold, saturated $NaHCO_3$. The organic extract was washed with water and brine, dried and concentrated to an oily residue which was purified by bulb-to-bulb distillation under reduced pressure, and then stored as a colorless oil over 4Å molecular sieves (675 mg, 70%): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.46 (d, J = 1.8 Hz, 1H), 6.70 (d, J = 1.8 Hz, 1H), 5.25 (hept, J = 6.3 Hz, 1H), 5.20 (hept, J = 6.3 Hz, 1H), 1.35 (d, J = 6.3 Hz, 6H), 1.34 (d, J = 6.3 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 161.8, 157.2, 144.1, 143.8, 124.1, 112.6, 69.3, 69.0, 21.57, 21.55; IR (KBr): ν = 1728 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{17}O_5$: 241.1071 [M+H$^+$]; found: 241.1079; elemental analysis calcd (%) for $C_{12}H_{16}O_5$: C 59.99, H 6.71; found: C 59.89, H 6.83.

Preparation of Me_3SnLi. MeLi (215 mol-%, 1.6 M in Et_2O) was added to a 0 °C solution of Me_6Sn_2 (220 mol-%) in THF (0.5 M). After 15 min, the solution was cooled to –78 °C and treated with a solution of the corresponding aromatic diester (100 mol-%) in THF (0.2 M).

Diisopropyl 4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*b*]furan-3a,6a-dicarboxylate (**9a**). A –78 °C solution of Me_3SnLi in THF was treated with a solution of **7** (120 mg, 0.50 mmol) in THF and stirred for 20 min, warmed to –50 °C and stirred for 40 min. 1,3-Diiodopropane (70 μL, 0.61 mmol) was added, and the mixture stirred for 3 h at –50 °C and then for 18 h while slowly warming to room temperature. The reaction was quenched by adding pH 5.6 acetate buffer (5 mL) and then partitioned between CH_2Cl_2 (10 mL) and acetate buffer (5 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product showed to be an inseparable mixture of starting furan and desired product so it was dissolved in a 1:1 dioxane-water mixture (4 mL) and treated with $LiOH\cdot H_2O$ (63 mg, 1.5 mmol). After stirring for 3 h at room temperature, pH 5.6 acetate buffer (15 mL) was added. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phase was washed with brine, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (neutral Al_2O_3, CH_2Cl_2/hexane 1:1) to give 89 mg (63%) of **9a** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.43 (d, J = 2.7 Hz, 1H), 4.98 (hept, J = 6.3 Hz, 1H), 4.90 (hept, J = 6.3 Hz, 1H), 4.76 (d, J = 2.7 Hz, 1H), 2.29-2.03 (m, 3H), 1.89-1.61 (m, 3H), 1.18 (m, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.3, 170.3, 147.0, 103.9, 97.3, 68.9, 68.5, 68.2, 39.9, 37.4, 23.5, 21.58, 21.56, 21.50, 21.46; IR (KBr): ν = 1729 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{22}O_5$: C 63.81, H 7.85; found: C 63.41, H 8.25.

Diisopropyl 3a,4,5,6,7,7a-hexahydrobenzofuran-3a,7a-dicarboxylate (**9b**). Following the procedure described above for **9a**, except using 1,4-diiodobutane (80 μL, 0.61 mmol), provided **9b** as a colorless oil (87 mg, 59%): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.35 (d, J = 2.7 Hz, 1H), 5.07 (hept, J = 6.3 Hz, 1H), 4.92 (m, 2H), 2.03 (m, 2H), 1.88 (m, 2H), 1.46 (m, 4H), 1.28 (d, J = 6.3 Hz, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.17 (d, J = 6.3 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.8, 170.8, 146.0, 106.4, 87.9, 68.4, 68.0, 57.2, 32.4, 29.1, 21.6, 21.41, 21.36, 21.3, 20.1, 19.2; IR (KBr): ν = 1729 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{25}O_5$: 297.1697 [M+H$^+$]; found: 297.1697; elemental analysis calcd (%) for $C_{16}H_{24}O_5$: C 64.84, H 8.16; found: C 64.51, H 8.18.

Diisopropyl 4,5,6,7,8,8a-hexahydro-3a*H*-cyclohepta[*b*]furan-3a,8a-dicarboxylate (**9c**). A –78 °C solution of Me_3SnLi in THF was treated with a solution of **7** (120 mg, 0.50 mmol) in THF and stirred for 1 h. 1,5-Diiodopentane (90 μL, 0.60 mmol) in DMF (2 mL) was added, and the reaction mixture was stirred for 14 h while warming from –78 °C to room temperature, and then at 40 °C for 6 h. Work-up as for **9a** afforded **9c** (74 mg, 48%) as a colorless oil after bulb-to-bulb distillation (0.01 mmHg, 80 °C): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.41 (d, J = 2.7 Hz, 1H), 4.92 (m, 2H), 4.83 (d, J = 2.7 Hz, 1H), 2.18 (m, 1H), 1.94 (m, 3H), 1.73-1.24 (m, 6H), 1.18 (m, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.7, 171.4, 144.6, 105.5, 92.7, 68.6, 68.4, 64.0, 35.3, 34.1, 30.7, 24.6, 22.8, 21.42, 21.38; IR (KBr): ν = 1737 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{26}O_5$: C 65.78, H 8.44; found: C 65.95, H 8.27.

Diethyl 4,5,6,6a-tetrahydro-3a*H*-cyclopenta[*b*]thiophene-3a,6a-dicarboxylate (**10a**). A –78 °C solution of Me_3SnLi in THF was treated with a solution of **8**[19] (105 mg, 0.46 mmol) in THF and stirred for 1 h. 1,3-Diiodopropane (60 μL, 0.52 mmol) was added, and the mixture stirred for 1 h at –78 °C and then for 14 h while slowly warming to room temperature. Work-up as for **9a** afforded **10a** (68 mg, 55%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.10 (dd, J = 6.1, 0.7 Hz, 1H), 5.56 (dd, J = 6.1, 0.5 Hz, 1H), 4.12 (m, 4H), 2.50 (m, 1H), 2.22 (m, 2H), 1.97 (m, 3H), 1.22 (t, J = 7.1 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.6, 172.3, 125.6, 124.9, 71.7, 71.6, 61.4, 61.0, 41.0, 39.2, 24.7, 13.9, 13.8; IR (KBr): ν = 1727 cm^{-1}; elemental analysis calcd (%) for $C_{13}H_{18}O_4S$: C 57.76, H 6.71, S 11.86; found: C 57.43, H 7.10, S 11.56.

Diethyl 3a,4,5,6,7,7a-hexahydrobenzo[*b*]thiophene-3a,7a-dicarboxylate (**10b**). A –78 °C solution of Me_3SnLi in THF was treated with **8**[19] (100 mg, 0.44 mmol) in THF and stirred for 1 h. 1,4-Diiodobutane (70 μL, 0.53 mmol) was added and the mixture stirred for 1 h at –78 °C, and then for 14 h while slowly warming up to room temperature. Work-up as for **9a** afforded **10b** (75 mg, 60%) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.99 (d, J = 6.3 Hz, 1H), 5.95 (d, J = 6.3 Hz, 1H), 4.13 (quint, J = 7.1 Hz, 4H), 2.18 (m, 2H), 2.00 (m, 1H), 1.69 (m, 3H), 1.48 (m, 1H), 1.33 (m, 1H), 1.22 (q, J = 7.2 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.1, 172.9, 130.9, 121.7, 63.0, 61.2, 60.8, 59.8, 33.7, 28.9, 21.1, 19.4, 14.1, 13.9; IR (KBr): ν = 1729 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{14}H_{20}O_4SNa$:

307.0975 [M+Na^+]; found: 307.0981; elemental analysis calcd (%) for $C_{14}H_{20}O_4S$: C 59.13, H 7.09, S 11.28; found: C 58.78, H 7.07, S 11.04.

Diethyl 3a,4,7,7a-tetrahydrobenzo[*b*]thiophene-3a,7a-dicarboxylate (10c). A –78 °C solution of Me_3SnLi in THF was treated with **8**[19] (92 mg, 0.40 mmol) in THF and stirred for 1 h. *cis*-1,4-Dichloro-2-butene (50 μL, 0.48 mmol) was added and the mixture stirred for 1 h at –78 °C, then slowly allowed to reach r.t. for 14 h, and heated at 30 °C for 3 h. Work-up as for **9a** afforded **10c** as a colorless oil (59 mg, 52%): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.05 (d, J = 6.3 Hz, 1H), 6.03 (d, J = 6.3 Hz, 1H), 5.86 (m, 1H), 5.77 (m, 1H), 4.14 (m, 4H), 2.84 (dquint, J = 19.0, 2.6 Hz, 1H), 2.74 (m, 1H), 2.49 (m, 2H), 1.22 (q, J = 7.3 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.9, 172.5, 131.6, 124.7, 124.4, 122.8, 61.7, 61.4, 60.9, 58.0, 34.0, 30.5, 13.9, 13.8; IR (KBr): ν = 1730 cm^{-1}; elemental analysis calcd (%) for $C_{14}H_{18}O_4S$: C 59.55, H 6.43, S 11.36; found: C 59.78, H 6.63, S 11.32.

Diisopropyl benzofuran-2,3-dicarboxylate (11). Toluene (25 mL) was added to a solution of benzofuran-2,3-dicarboxylic acid (1 g, 4.85 mmol) in *i*PrOH (25 mL) in the presence of H_2SO_4 (150 μL), and the mixture was refluxed using a Dean-Stark trap. During the first 6 hours, 6 mL were withdrawn every hour and replenished by an equal volume of the *i*PrOH-toluene mixture. After 36 hours, the solution was evaporated under reduced pressure to 5 mL, diluted with CH_2Cl_2 (20 mL) and neutralized with cold, saturated $NaHCO_3$. The organic layer was washed with brine, dried and concentrated. The residue was purified by bulb-to-bulb distillation to yield **11** as a colorless oil (1.21 g, 86%): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.85 (d, J = 7.8 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.45 (m, 1H), 7.35 (m, 1H), 5.33 (m, 2H), 1.42 (d, J = 6.3 Hz, 6H), 1.40 (d, J = 6.3 Hz, 6H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 162.0, 158.3, 153.9, 145.7, 127.7, 125.4, 124.4, 122.5, 118.3, 112.1, 70.1, 69.3, 21.8, 21.7; IR ($CHCl_3$): ν = 1728 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{16}H_{19}O_5$: 291.1227 [M+H^+]; found: 291.1232; elemental analysis calcd (%) for $C_{16}H_{18}O_5$: C 66.19, H 6.25; found: C 66.22, H 6.52.

Diisopropyl 2,3,3a,8b-tetrahydro-1*H*-benzo[*b*]cyclopenta[*d*]furan-3a,8b-dicarboxylate (12a). A –78 °C solution of Me_3SnLi in THF was treated with a solution of **11** (110 mg, 0.38 mmol) in THF (2 mL), warmed to –55 °C and stirred for 1 h. 1,3-Diiodopropane (50 μL, 0.44 mmol) was added and the mixture stirred for 15 h while slowly warming to room temperature, and then heated at 30 °C for 3 h. The reaction was quenched by adding pH 5.6 acetate buffer and then partitioned between CH_2Cl_2 and acetate buffer. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography (Al_2O_3, CH_2Cl_2/hexane 3:1) to give 88 mg (70%) of **12a** as a white solid: m.p. 82-85 °C (EtOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.12 (m, 2H), 6.86 (m, 2H), 5.03 (hept, J = 6.3 Hz, 1H), 4.91 (hept, J = 6.3 Hz, 1H), 2.48 (td, J = 12.8, 6.4 Hz, 1H), 2.26 (m, 3H), 1.83 (m, 1H), 1.49 (m, 1H), 1.24 (d, J = 6.1 Hz, 3H), 1.22 (d, J = 6.1 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.0, 170.4, 159.4, 129.2, 128.9, 123.3, 121.2, 109.8, 98.5, 69.1, 68.8, 67.8, 40.4, 38.3, 23.8, 21.6, 21.5, 21.32, 21.31; IR ($CHCl_3$): ν = 1734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{25}O_5$: 333.1693 [M+H^+]; found: 333.1699; elemental analysis calcd (%) for $C_{19}H_{24}O_5$: C 68.66, H 7.28; found: C 68.38, H 7.68.

Diisopropyl 1,2,3,4,4a,9b-hexahydrodibenzo[*b*,*d*]furan-4a,9b-dicarboxylate (12b). Using the same procedure as for **12a**, except that 1,4-diiodobutane (60 μL, 0.45 mmol) was used as the electrophile, **12b** was obtained as a white solid (89 mg, 68%): mp 84-86 ºC (EtOH); ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.20 (m, 2H), 6.92 (td, J = 7.6, 0.9 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 5.06 (hept, J = 6.3 Hz, 1H), 4.83 (hept, J = 6.2 Hz, 1H), 2.42 (dt, J = 14.2, 4.1 Hz, 1H), 2.14 (m, 2H), 1.70 (m, 2H), 1.51 (m, 3H), 1.27 (d, J = 6.3 Hz, 3H), 1.23 (d, J = 6.3 Hz, 3H), 1.09 (d, J = 6.2 Hz, 3H), 1.08 (d, J = 6.2 Hz, 3H). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.7, 170.5, 157.6, 129.3, 129.0, 123.4, 121.1, 111.3, 89.7, 68.8, 68.5, 57.1, 33.2, 29.2, 21.7, 21.5, 21.3, 21.2, 20.7, 20.3; HRMS (ESI): *m/z* calcd for $C_{20}H_{26}O_5$+Na^+: 369.1672 [M+Na^+]; found: 369.1678.

Diisopropyl 6,7,8,9,10,10a-hexahydro-5a*H*-benzo[*b*]cyclohepta[*d*]furan-5a,10a-dicarboxylate (12c). A –78 °C solution of Me_3SnLi in THF was treated with a solution of **11** (102 mg, 0.35 mmol) in THF, then warmed to –55 °C and stirred for 1.5 h. 1,5-Diiodopentane (60 μL, 0.40 mmol) in DMF (1.2 ml) was added, and the mixture stirred for 8 h while slowly warming to room temperature, and then heated at 45 °C for 14 h. Work-up as for **12a** and purification by column chromatography (neutral Al_2O_3, CH_2Cl_2/Hex 1:2) afforded 75 mg (59%) of **12c** as a white solid: mp 81-84 ºC (EtOH); ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.16 (m, 2H), 6.89 (td, J = 7.5, 1.0 Hz, 1H), 6.83 (d, J = 8.0 Hz, 1H), 4.90 (m, 2H), 2.41-2.03 (m, 4H), 1.73-1.12 (m, 15H), 1.04 (d, J = 6.2 Hz, 3H); ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 173.0, 171.4, 158.9, 130.6, 129.5, 124.9, 121.1, 109.7, 95.4, 69.4, 69.3, 63.7, 36.4, 35.4, 31.2, 25.0, 23.2, 21.8, 21.7, 21.6, 21.5; IR (KBr): ν = 1734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{21}H_{29}O_5$: 361.2010 [M+H^+]; found: 361.2010; elemental analysis calcd (%) for $C_{21}H_{28}O_5$: C 69.98, H 7.83; found: C 69.58, H 7.82.

Diisopropyl 1,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-4a,9b-dicarboxylate (12d). Compound **12d** was prepared following the same procedure as for **12a**. Thus, **11** (120 mg, 0.41 mmol) and *cis*-1,4-dichloro-2-butene (50 μL, 0.48 mmol) afforded 85 mg of **12d** (60%) as a white solid, after work-up and purification by column chromatography (neutral Al_2O_3, CH_2Cl_2/Hex 1:1): mp 79-81 ºC (EtOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.11 (m, 2H), 6.82 (m, 2H), 5.79 (m, 2H), 5.04 (hept, J = 6.3 Hz, 1H), 4.91 (hept, J = 6.3 Hz, 1H), 2.73 (m, 4H), 1.23 (d, J = 6.3 Hz, 3H), 1.21 (d, J = 6.3 Hz, 3H), 1.13 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.3 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.5, 170.5, 159.1, 129.8, 129.1, 126.7, 125.4, 123.3, 121.0, 109.9, 91.7, 69.1, 69.0, 59.4, 33.9, 31.7, 21.5, 21.4, 21.2; IR (KBr): ν = 1762, 1725 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{24}O_5$: C 69.75, H 7.02; found: C 69.45, H 7.02.

Diisopropyl naphthalene-1,4-dicarboxylate (13). A suspension of naphthalene-1,4-dicarboxylic acid (1.0 g, 4.62 mmol) and benzyltriethylamonium chloride (25 mg, 0.11 mmol) in 1,2-dichloroethane (8 mL) was heated to reflux and then treated with $SOCl_2$ (870 μL, 12 mmol). The reaction mixture was refluxed for 12 h, hot filtered, and the filtrate concentrated. The residue was dried under vacuum in the presence of NaOH pellets. The crude acid chloride was dissolved in CH_2Cl_2 (24 mL), DMAP (56 mg, 0.46 mmol) and *i*PrOH (1.5 mL, 19 mmol) were added, and the resulting solution was cooled down to 0 °C and treated with Et_3N (2.7 mL, 19 mmol). The reaction mixture was stirred for 15 min at 0 °C and at room temperature for 4 h. Then it was washed with HCl 2M and water, and the organic layer was dried and concentrated. Column chromatography (EtOAc/Hexane 1:20) afforded 1.18 g of **13** (85% yield) as a white solid: mp 69-70 °C (CH_2Cl_2-hexane); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.78 (dd, J = 6.7, 3.4 Hz, 2H), 8.02 (s, 2H), 7,61 (dd, J = 6.7, 3.4 Hz, 2H), 5.37 (hept, J = 6.3 Hz, 2H), 1.43 (d, J = 6.3 Hz, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.9, 132.3, 131.3, 127.6, 127.5, 125.9, 69.1, 21.9; IR (KBr): ν = 1713 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{20}O_4$: C 71.98, H 6.71; found: C 71.78, H 7.01.

Diisopropyl naphthalene-2,6-dicarboxylate (14). Using the same procedure as for **13**, naphthalene-2,6-dicarboxylic acid (500 mg, 2.3 mmol) afforded 615 mg of **14** (89% yield): mp 118-120 °C (CH_2Cl_2-hexane); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.59 (s, 2H), 8.10 (dd, J = 8.5, 1.0 Hz, 2H), 7.98 (d, J = 8.5 Hz, 2H), 5.31 (hept, J = 6.2 Hz, 2H), 1.41 (d, J = 6.2 Hz, 12H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 165.9, 134.5, 130.4, 130.1, 129.4, 126.0, 68.8, 22.0; IR (KBr): ν = 1708 cm^{-1}; elemental analysis calcd (%) for $C_{18}H_{20}O_4$: C 71.98, H 6.71; found: C 71.70, H 7.00.

Diisopropyl 2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-5,9b-dicarboxylate (15a). A –78 °C solution of Me_3SnLi (0.77 mmol) in THF was treated with a solution of **13** (109 mg, 0.36 mmol) in THF (2 mL). After stirring for 4 h, 1,3-dibromopropane (40 μL, 0.40 mmol) was added and the resulting mixture was stirred for 2 h at –78 °C and then for 18 h while slowly warming to room temperature. The reaction was quenched with pH 7.0 phosphate buffer (0.2 mL), and then partitioned between

CH_2Cl_2 and phosphate buffer. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was washed with brine, dried and concentrated. The residue was purified by column chromatography (70-230 SiO_2, EtOAc/hexane 1:20) to give **15a** as a colorless oil (108 mg, 87%): ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.83 (m, 1H), 7.24 (m, 3H), 6.82 (d, J = 4.7 Hz, 1H), 5.17 (hept, J = 6.3 Hz, 1H), 4.95 (hept, J = 6.3 Hz, 1H), 3.31 (m, 1H), 2.57 (m, 1H), 2.04 (m, 2H), 1.63 (m, 3H), 1.33 (d, J = 6.3 Hz, 6H), 1.16 (d, J = 6.2 Hz, 3H), 1.14 (d, J = 6.2 Hz, 3H); ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 175.1, 166.8, 140.4, 136.8, 129.1, 129.0, 128.5, 127.5, 127.3, 126.7, 69.0, 68.6, 56.7, 43.8, 38.6, 33.0, 23.3, 22.2, 21.8, 21.7; IR (KBr): ν = 1717 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{26}O_4$: C 73.66, H 7.65; found: C 73.91, H 7.82.

Diisopropyl 6a,7,12,12a-tetrahydrotetraphene-5,12a-dicarboxylate (15b). Using the same procedure as for **15a**, except that 1,2-*ortho*-dichloroxylene (65 mg, 0.37 mmol) was used as the electrophile, 101 mg of **13** (0.34 mmol) afforded 82 mg of **15b** (60%) as a colorless oil: ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.86 (m, 1H), 7.29 (m, 2H), 7.12 (m, 5H), 6.92 (d, J = 3.4 Hz, 1H), 5.11 (hept, J = 6.3 Hz, 2H), 3.56 (m, 1H), 3.26 (d, J = 16.9 Hz, 1H), 3.07 (m, 2H), 2.85 (dd, J = 17.4, 3.8 Hz, 1H), 1.31 (d, J = 6.2 Hz, 6H), 1.22 (d, J = 6.3 Hz, 3H), 1.14 (d, J = 6.3 Hz, 3H). ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 174.6, 165.9, 143.3, 138.9, 136.7, 133.9, 131.6, 130.2, 129.6, 129.0, 128.8, 127.7, 127.5, 126.4, 126.3, 125.7, 69.4, 68.9, 50.8, 36.6, 34.2, 31.7, 22.2, 22.1, 22.0, 21.7; IR (KBr): ν = 1756 cm^{-1}; HRMS (ESI): m/z calcd for $C_{26}H_{29}O_4$: 405.2066 [M+H$^+$]; found: 405.2102.

Diisopropyl 2,3,3a,9b-tetrahydro-1*H*-cyclopenta[*a*]naphthalene-3a,7-dicarboxylate (**16a**). Following the same procedure as for **15a**, starting from **14** (103 mg, 0.34 mmol) and using 1,3-dibromopropane (40 μL, 0.39 mmol) as the electrophile, **16a** was obtained as a colorless oil (93 mg, 79%): ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.80 (dd, J = 7.8, 1.6 Hz, 1H), 7.73 (s, 1H), 7.23 (d, J = 7.8 Hz, 1H), 6.49 (d, J = 9.6 Hz, 1H), 5.81 (d, J = 9.6 Hz, 1H), 5.19 (hept, J = 6.3 Hz, 1H), 4.88 (hept, J = 6.3 Hz, 1H), 3.61 (t, J = 9.1 Hz, 1H), 2.41-2.10 (m, 2H), 2.01 (m, 1H), 1.62 (m, 3H), 1.34 (d, J = 6.2 Hz, 6H), 1.13 (t, J = 6.7 Hz, 6H); ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 174.8, 166.3, 143.5, 131.3, 131.1, 129.8, 129.0, 128.4, 128.1, 126.4, 68.7, 68.5, 53.5, 45.9, 40.2, 37.0, 23.9, 22.2, 21.88, 21.85; IR (KBr): ν = 1717 cm^{-1}; elemental analysis calcd (%) for $C_{21}H_{26}O_4$: C 73.66, H 7.65; found: C 73.56, H 8.00.

Diisopropyl 4b,5,6,7,8,8a-hexahydrophenanthrene-2,8a-dicarboxylate (**16b**). Following the same procedure as for **15a**, but starting from **14** (92 mg, 0.31 mmol) and using 1.4-diiodobutane (46 μL, 0.35 mmol) as the electrophile, **16b** was obtained in 66% yield (72 mg) as a colorless oil: ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.80 (dd, J = 7.8, 1.7 Hz, 1H), 7.69 (d, J = 1.7 Hz, 1H), 7.19 (d, J = 7.8 Hz, 1H), 6.60 (d, J = 9.5 Hz, 1H), 5.78 (dd, J = 9.5, 1.0 Hz, 1H), 5.19 (hept, J = 6.3 Hz, 1H), 4.77 (hept, J = 6.3 Hz, 1H), 3.22 (m, 1H), 2.00 (m, 1H), 1.63 (m, 3H), 1.39 (m, 4H), 1.33 (d, J = 6.3 Hz, 6H), 1.04 (d, J = 6.3 Hz, 3H), 1.03 (d, J = 6.3 Hz, 3H); ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 175.0, 166.3, 146.2, 132.3, 132.1, 129.8, 129.3, 128.5, 127.8, 127.7, 68.6, 68.2, 47.9, 42.4, 34.5, 30.3, 24.6, 22.5, 22.2, 21.75, 21.74; IR (KBr): ν = 1716 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{28}O_4$: C 74.13, H 7.92; found: C 73.87, H 7.56.

((4b*S*,8a*S*)-4b,5,6,7,8,8a-hexahydrophenanthrene-2,8a-diyl)dimethanol (**16c**). A 0 ºC suspension of $LiAlH_4$ (20 mg, 0.53 mmol) in THF (1 mL) was treated with a solution of **16b** (90 mg, 0.25 mmol) in THF (1 mL). The reaction mixture was stirred for 12 h while slowly warming to room temperature. After cooling down to 0 ºC, EtOAc (1 mL) was carefully added, followed by $CHCl_3$, saturated aqueous Na_2CO_3, solid KH_2PO_4 and Na_2SO_4. The resulting suspension was stirred at room temperature for 1h, then filtered over celite and evaporated. The product was obtained as white crystals after crystallization from CH_2Cl_2/hexanes (47 mg, 77%): mp 100-101 ºC; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.11 (dd, J = 7.6, 1.5 Hz, 1H), 7.04 (m, 2H), 6.52 (d, J = 9.6 Hz, 1H), 5.58 (dd, J = 9.6, 1.3 Hz, 1H), 4.59 (s, 2H), 3.28 (d, J = 10.7 Hz, 1H), 3.14 (d, J = 10.7 Hz, 1H), 2.60 (dd, J = 11.8, 3.8 Hz, 1H), 1.86 (br s, 1H), 1.71-1.18 (m, 9H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 139.7, 138.9, 134.0, 132.1, 128.9, 127.9, 126.4, 125.2, 69.1, 65.2, 41.4, 32.8, 31.1, 24.8, 22.6; elemental analysis calcd (%) for $C_{16}H_{20}O_2$: C 78.65, H 8.25; found: C 78.58, H 8.25.

Methyl 4-(1-(4-methoxyphenylamino)butyl)benzoate (18a). A solution of Me_3SnLi (0.83 mmol) in THF was treated with a solution of **17**[29] (102 mg, 0.38 mmol) in THF (4 mL) at –78 °C. After stirring for 2 h, 1-iodopropane (46 μL, 0.47 mmol) was added and the resulting mixture was stirred for 2 h at –78 °C. The reaction mixture was quenched with deoxygenated pH 7.0 phosphate buffer, and then partitioned between CH_2Cl_2 and phosphate buffer. The aqueous phase was extracted with CH_2Cl_2, and the combined organic phase was washed with brine, dried, and concentrated. The residue was purified by column chromatography (neutral Al_2O_3, CH_2Cl_2/hexane 2:1 to 3:1) to give **18a** as a colorless oil (93 mg, 78%): ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.95 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.2 Hz, 2H), 6.64 (m, 2H), 6.43 (m, 2H), 4.31 (t, J = 6.8 Hz, 1H), 3.93 (m, 1H), 3.86 (s, 3H), 3.64 (s, 3H), 1.74 (m, 2H), 1.37 (m, 2H), 0.93 (t, J = 7.3 Hz, 3H); ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 167.3, 152.5, 151.0, 142.0, 130.2, 129.5, 127.1, 115.1, 114.8, 59.0, 56.1, 52.4, 41.4, 20.0, 14.3; IR (KBr): ν = 1706 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{23}NO_3$: C 72.82, H 7.40, N 4.47; found: C 72.56, H 7.60, N 4.61.

Methyl 4-[((4-methoxyphenyl)methylamino)methyl]benzoate (18b). A solution of Me_3SnLi (0.80 mmol) in THF was treated with a solution of **17**[29] (98 mg, 0.36 mmol) in THF (4 mL) at –78 °C. After stirring for 2 h, Me_2SO_4 (45 μL, 0.47 mmol) was added and the resulting mixture was stirred for 2 h at –78 °C, then slowly warmed to room temperature for 4 h, and stirred 4 more h at this temperature. Work-up and purification as for **18a** afforded **18b** as a yellowish oil that was recrystallized from CH_2Cl_2/hexane to give a white solid (63 mg, 60%): mp 57-58 ºC (CH_2Cl_2/hexane); ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.96 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.79 (d, J = 9.0 Hz, 2H), 6.70 (d, J = 9.0 Hz, 2H), 4.48 (s, 2H), 3.86 (s, 3H), 3.72 (s, 3H), 2.94 (s, 3H); ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 167.3, 152.5, 145.7, 144.9, 130.2, 129.5, 127.6, 115.1, 114.9, 58.3, 56.1, 52.4, 39.8; IR (KBr): ν = 1720 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{19}NO_3$: C 71.56, H 6.71, N 4.91; found: C 71.30, H 6.48, N 5.00.

Methyl 4-(1-(4-methoxyphenyl)pyrrolidin-2-yl)benzoate (18c). A solution of Me_3SnLi (0.77 mmol) in THF was treated with a solution of **17**[29] (95 mg, 0.35 mmol) in THF (4 mL) at –78 °C. After stirring for 2 h, 1,3-dibromopropane (40 μL, 0.39 mmol) was added and the resulting mixture was stirred for 1 h at –78 °C, and then 4 h while warming to room temperature. Work-up as for **18a**, followed by column chromatography purification (neutral Al_2O_3, EtOAc/hexane 1:6), afforded **18c** as a white solid (96 mg, 87%): mp 79-80 ºC (CH_2Cl_2/hexane); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.96 (d, J = 8.3 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 6.39 (d, J = 9.0 Hz, 2H), 4.64 (dd, J = 8.5, 1.9 Hz, 1H), 3.88 (s, 3H), 3.70 (m, 1H), 3.69 (s, 3H), 3.35 (dd, J = 16.1, 8.3 Hz, 1H), 2.39 (m, 1H), 1.93 (m, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 167.0, 151.0, 150.7, 141.8, 129.9, 128.6, 126.0, 114.8, 113.0, 63.3, 55.8, 52.0, 49.7, 36.1, 23.3; IR (KBr): ν = 1720, 1713 cm^{-1}; elemental analysis calcd (%) for $C_{19}H_{21}NO_3$: C 73.29, H 6.80, N 4.50; found: C 72.99, H 7.09, N 4.46.

Methyl 4-(1-(4-methoxyphenyl)piperidin-2-yl)benzoate (18d). Following the same procedure as for **18c**, but starting from **17**[29] (105 mg, 0.39 mmol) and using 1.4-diiodobutane (62 μL, 0.47 mmol) as the electrophile. The reaction mixture was stirred for 2 h at –78 °C and then 4 more h while warming to room temperature. Work-up and purification as for **18a**, gave **18d** as a white solid (95 mg, 75%): mp 83-84 °C (CH_2Cl_2-hexane); ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.81 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 6.90 (m, 2H), 6.64 (m, 2H) 4.06 (dd, J = 9.7, 2.9 Hz, 1H), 3.81 (s, 3H), 3.64 (s, 3H), 3.34 (m, 1H), 2.80 (m, 1H), 1.94-1.42 (m, 6H); ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 167.3, 155.7, 151.3, 146.7, 129.8, 128.8, 128.1, 125.0, 114.2, 65.0, 57.9, 55.7, 52.3, 37.1, 27.1, 24.9; IR (KBr): ν = 1721 cm^{-1}; elemental analysis calcd (%) for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30; Found: C 73.42, H 7.46, N 4.27.

Methyl 4-(1-(4-methoxyphenyl)-6-oxopiperidin-2-yl)benzoate (18e). Following the same procedure as for **18c**, but starting from **17**[29] (100 mg, 0.37 mmol), using methyl 4-iodobutyrate (102 mg, 0.45 mmol) as the electrophile, and stirring for 2 h at –78 °C, 4 h while warming to room temperature, and then 14 h at 45 °C. Work-up and purification as for **18a**, gave **18d** as a white solid (84 mg, 67%): mp 82 °C (dec.) (CH_2Cl_2-hexane); ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.94 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 7.01 (d, J = 8.7 Hz, 2H), 6.74 (d, J = 8.7 Hz, 2H), 5.01 (t, J = 5.1 Hz, 1H), 3.86 (s, 3H), 3.70 (s, 3H), 2.63 (m, 2H), 2.34 (m, 1H), 1.90 (m. 3H); ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 171.1, 167.0, 158.5, 147.5, 135.5, 130.1, 130.0, 129.1, 127.7, 114.4, 65.6, 55.8, 52.5, 33.2, 32.8, 18.4; IR (KBr): ν = 1718, 1707 cm^{-1}. HRMS (ESI): m/z calcd for $C_{20}H_{22}NO_4$: 340.1549 [M+H$^+$]; found: 340.1543.

Procedure Using Substoichiometric Sn-reagent

Small pieces of lithium wire (56 mg, 8 mmol) were suspended in dry THF (1 mL) at room temperature, and Me_3SnCl (40 μL, 0.04 mmol) was added. After being stirred for 30 min, the suspension was cooled to –78 °C and treated with a solution of the corresponding diester (0.4 mmol) in THF (1 mL). After 16 h at –78 °C, the solution was transferred[30] via cannula to a flask cooled to –78 °C, and then treated with the corresponding electrophile, the reaction mixture was stirred for 6h while slowly warming to room temperature. Work-up as for **18a** and column chromatography purification (SiO_2, EtOAc/hexane 1:20) afforded the corresponding bicycles **21a**[10] (90 mg, 77% yield), **21b**[10] (83 mg, 68%), **22a**[10] (SiO_2, EtOAc/hexane 1:10, 73 mg, 60%) and **10b** (neutral Al_2O_3, CH_2Cl_2/hexane 1:1, 64 mg, 56%).

5-Methyl 2-(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl pyridine-2,5-dicarboxylate (24e). A suspension of 2-carboxy-5-methoxycarbonylpyridine[31] (**23**, 200 mg, 1.10 mmol) in CH_2Cl_2 (6 mL) was treated with (-)-8-phenylmenthol (256 mg, 1.10 mol), DMAP (22 mg, 0.18 mmol) and EDC (238 mg, 1.24 mmol) at room temperature. The reaction mixture was refluxed in a sealed tube and, each 48 h, more EDC (238 mg, 1.24 mmol) and DMAP (22 mg, 0.18 mmol) were added. After being refluxed for 7 days, the resulting solution was cooled to room temperature and washed with water and satd aqueous NaCl. The organic phase was dried (Na_2SO_4) and evaporated. Column chromatography of the residue (SiO_2, EtOAc/Hexane 1:6) afforded **24e** (354 mg, 81%) as a white solid after recrystallization from MeOH: mp: 131-133 ºC; ^{1}H NMR (250 MHz, $CDCl_3$): δ = 9.15 (dd, J = 2.1, 0.7 Hz, 1H), 8.14 (dd, J = 8.1, 2.1 Hz, 1H), 7.22 (m, 3H), 6.99 (t, J = 7.7 Hz, 2H), 6.80 (t, J = 7.3 Hz, 1H), 5.14 (td, J = 10.8, 4.5 Hz, 1H), 3.93 (s, 3H), 2.24 (td, J = 12.1, 3.6 Hz, 1H), 1.95 (m, 1H), 1.83 (m, 1H), 1.68 (m, 1H), 1.51 (m, 1H), 1.29 (s, 3H), 1.17 (s, 3H), 1.15 (m, 2H), 0.91 (m, 1H), 0.85 (d, J = 6.5 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 164.9, 162.9, 151.5, 150.7, 150.3, 137.6, 127.8, 127.7, 125.1, 124.7, 124.3, 75.9, 52.6, 50.2, 41.4, 39.4, 34.4, 31.2, 29.2, 26.3, 23.5, 21.7; elemental analysis calcd (%) for $C_{24}H_{29}NO_4$: C 72.89, H 7.39, N 3.54; found: C 72.76, H 7.47, N 3.64.

(*R*)-6-Methyl 8a-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] 1,2,3,8a-tetrahydroindolizine-6,8a-dicarboxylate (25e). A solution of Me_3SnLi (0.40 mmol) in THF was treated with a solution of **24e** (70 mg, 0.18 mmol) in THF at –78 °C. After stirring for 45 min, 1,3-dibromopropane (25 μL, 0.25 mmol) was added. The reaction mixture was stirred for 12 h while slowly warming to room temperature. Work-up as for **15a**, followed by column chromatography purification (SiO_2, EtOAc/hexane 1:6), afforded **25e** as a white solid (61 mg, 79%) after crystallization from Et_2O/CH_2Cl_2: mp 130-133 ºC; ^{1}H NMR (750 MHz, $CDCl_3$): δ = 7.48 (s, 1H), 7.19 (m, 4H), 7.08 (m, 1H), 6.42 (dd, J = 9.5, 1.0 Hz, 1H), 4.88 (d, J = 9.5 Hz, 1H), 4.66 (td, J = 10.6, 4.4 Hz, 1H), 3.65 (m, 1H), 3.62 (s, 3H), 3.49 (dt, J = 10.4, 7.6 Hz, 1H), 2.32 (m, 1H), 1.97 (m, 1H), 1.84 (ddd, J = 12.3, 10.6, 3.5 Hz, 1H), 1.74 (m, 3H), 1.44 (m, 1H), 1.31 (m, 2H), 1.22 (s, 3H), 1.17 (s, 3H), 0.88 (m, 2H), 0.77 (d, J = 6.5 Hz, 3H), 0.68 (ddd, J = 25.0, 13.0, 3.5 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.9, 166.8, 150.1, 143.3, 127.9, 125.8, 125.3, 123.3, 109.3, 98.8, 76.3, 68.7, 51.1, 50.7, 50.2, 41.2, 40.2, 37.6, 34.4, 31.2, 30.1, 27.2, 24.4, 21.7, 20.9; IR (KBr): ν = 1728, 1692 cm^{-1}; elemental analysis calcd (%) for $C_{27}H_{35}NO_4$: C 74.11, H 8.06, N 3.20; found: C 74.16, H 8.19, N 3.17.

(*R*)-7-Methyl 9a-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] 2,3,4,9a-tetrahydro-1*H*-quinolizine-7,9a-dicarboxylate (26e). 26e was prepared from **24e** (56 mg, 0.14 mmol) following the above procedure but using 1,4-dibromobutane (44 μL, 0.36 mmol) as the electrophile at –78 °C for 1 h, then DMF (1 mL) was added and, after 20 min, the cooling bath was removed and the reaction mixture was allowed to reach room temperature, and then heated at 60 °C for 12 h. Work-up as for **15a**, followed by column chromatography purification (SiO_2, EtOAc/hexane 1:6), afforded **26e** as a pale yellow oil in 58% yield (37 mg): ^{1}H NMR (750 MHz, $CDCl_3$): δ = 7.26 (m, 5H), 7.14 (m, 1H), 6.28 (dd, J = 9.8, 1.3 Hz, 1H), 4.81 (td, J = 10.6, 4.3 Hz, 1H), 4.50 (d, J = 9.8 Hz, 1H), 3.64 (s, 3H), 3.57 (td, J = 13.1, 3.3 Hz, 1H), 3.18 (m, 1H), 2.08 (m, 1H), 1.97 (m, 2H), 1.72 (m, 2H), 1.62 (m, 1H), 1.54 (m, 2H), 1.41 (m, 2H), 1.30 (m, 1H), 1.29 (s, 3H), 1.20 (s, 3H), 0.97 (m, 2H), 0.84 (d, J = 6.6 Hz, 3H), 0.77 (ddd, J = 25.0, 13.0, 3.5 Hz, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 170.1, 166.6, 150.5, 148.3, 128.0, 125.6, 125.3, 122.5, 113.5, 95.7, 76.8, 65.6, 52.4, 50.6, 49.8, 41.6, 40.1, 35.6, 34.4, 31.3, 29.0, 27.2, 25.5, 25.1, 21.8, 21.3; IR (KBr): ν = 1726, 1689 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{37}NO_4$: C 74.47, H 8.26, N 3.10; found: C 74.62, H 8.46, N 3.15.

(*R*)-3-Methyl 10a-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] 6,7,8,9,10,10a-hexahydropyrido[1,2-*a*]azepine-3,10a-dicarboxylate (27e). 27e was prepared from **24e** (50 mg, 0.13 mmol) following the above procedure but using 1,5-diiodopentane (25 μL, 0.17 mmol) as the electrophile at –78 °C for 1 h, then DMF (1 mL) was added and, after 20 min, the cooling bath was removed and the reaction mixture was allowed to reach room temperature, and then heated at 60 °C for 12 h. Work-up as for **15a**, followed by column chromatography purification (SiO_2, EtOAc/hexane 1:6) afforded **27e** as a pale yellow oil in 62% yield (37 mg): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.38 (s, 1H), 7.26 (m, 4H), 7.14 (m, 1H), 6.47 (dd, J = 9.6, 1.2 Hz, 1H), 4.76 (td, J = 10.6, 4.4 Hz, 1H), 4.59 (d, J = 9.6 Hz, 1H), 3.66 (s, 3H), 3.29 (m, 2H), 2.12-1.14 (m, 19H), 0.96 (m, 2H), 0.82 (d, J = 6.4 Hz, 3H), 0.75 (m, 1H); ^{13}C NMR (62.9 MHz, $CDCl_3$, main isomer): δ = 172.7, 166.6, 150.4, 147.3, 128.0, 125.7, 125.3, 124.5, 113.5, 97.4, 76.4, 67.7, 53.3, 50.6, 50.1, 41.6, 40.4, 40.2, 34.4, 31.3, 31.2, 29.5, 29.0, 27.2, 25.0, 22.4, 21.7; IR (KBr): ν = 1729, 1690 cm^{-1}; elemental analysis calcd (%) for $C_{29}H_{39}NO_4$: C 74.81, H 8.44, N 3.01; found: C 75.15, H 8.34, N 3.12.

6-(Methoxycarbonyl)quinoline-2-carboxylic acid. To a stirred solution of dimethyl quinoline-2,6-dicarboxylate[32] (1.75 g, 7.1 mmol) in 45 mL of dioxane at room temperature was added a solution of LiOH·H_2O (300 mg, 7.1 mmol) in H_2O (5.6 mL). After stirring for 16 h the reaction mixture was filtered, and the filtrate was washed with dioxane. The solid was dissolved in water, and the aqueous solution was cooled to 0 ºC and acidified with HCl. The precipitate was isolated by filtration and washed once with water giving 1.40 g of the product as a white powder after drying (85%): ^{1}H NMR (250 MHz, CD_3OD): δ = 8.74 (s, 1H), 8.65 (d, J = 8.5 Hz, 1H), 8.41-8.22 (m, 3H), 4.00 (s, 3H); ^{13}C NMR (62.9 MHz, DMSO-D_6): δ = 166.0, 165.7, 150.7, 148.3, 139.5, 130.8, 130.2, 129.3, 129.0, 128.1, 121.6, 52.7; IR (KBr): ν = 1724 cm^{-1}; elemental analysis calcd (%) for $C_{12}H_9NO_4$: C 62.34, H 3.92, N 6.06; found: C 62.62, H 3.98, N 6.31.

6-Methyl 2-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] quinoline-2,6-dicarboxylate (**28**). A suspension of 6-(methoxycarbonyl)quinoline-2-carboxylic acid (700 mg, 3.0 mmol) in CH_2Cl_2 (20 mL) was treated with (-)-8-phenylmenthol (705 mg, 3.0 mol), DMAP (135 mg, 1.1 mmol) and di(2-pyridyl) carbonate (DPC) (820 mg, 3.8 mmol) at room temperature. The reaction mixture was refluxed in a sealed tube and, after 24 h, more DPC (650 mg, 3.0 mmol) and DMAP (135 mg, 1.1 mmol) were added. After being refluxed for 4 days, the resulting solution was cooled to room temperature, pH 7.0 phosphate buffer was added and the mixture was extracted twice with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and evaporated. Flash column chromatography of the

residue (SiO_2, EtOAc/Hexane 1:10) afforded **28** (1.16 g, 85%) as a white foam: ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 8.61 (d, J = 2.0 Hz, 1H), 8.25 (m, 3H), 7.43 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 7.6 Hz, 2H), 7.02 (t, J = 7.5 Hz, 2H), 6.79 (t, J = 7.3 Hz, 1H), 5.15 (td, J = 10.7, 4.4 Hz, 1H), 3.98 (s, 3H), 2.29 (ddd, J = 12.1, 10.4, 3.6 Hz, 1H), 2.05 (m, 1H), 1.90-1.49 (m, 3H), 1.38 (s, 3H), 1.26 (s, 3H), 1.23 (m, 2H), 0.98 (m, 1H), 0.92 (d, J = 6.4 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 166.1, 163.3, 151.5, 149.7, 149.0, 137.9, 131.0, 130.3, 129.4, 129.1, 128.0, 127.8, 125.1, 124.7, 121.6, 76.1, 52.4, 50.3, 41.4, 39.5, 34.4, 31.2, 28.7, 26.4, 24.1, 21.7; IR (KBr): ν = 1726 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{31}NO_4$+Na^+: 468.2145 [M+Na^+]; found: 468.2149; elemental analysis calcd (%) for $C_{28}H_{31}NO_4$: C 75.48, H 7.01, N 3.14; found: C 75.08, H 6.90, N 3.03.

(*R*)-6-Methyl 2-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] 2-propyl-1,2-dihydroquinoline-2,6-dicarboxylate (**29a**). A –78 ºC solution of Me_3SnLi (0.62 mmol) in THF (0.7 mL) was treated with a solution of **28** (127 mg, 0.28 mmol) in THF (2.1 mL). After 1h, 1-iodopropane (50 μL, 0.44 mmol) was added. The reaction mixture was stirred for 8 h while slowly warming to room temperature. Work-up as for **15a** followed by column chromatography (SiO_2, EtOAc/Hexane 1:10) afforded **29a** (125 mg, 90%) as a white foam: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.66 (dd, J = 8.4, 2.0 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.34 (d, J = 4.2 Hz, 4H), 7.23 (m, 1H), 6.32 (d, J = 9.8 Hz, 1H), 6.31 (d, J = 8.3 Hz, 1H), 5.36 (dd, J = 9.8, 2.1 Hz, 1H), 4.79 (td, J = 10.7, 4.3 Hz, 1H), 3.82 (s, 3H), 3.77 (s, 1H), 2.12 (ddd, J = 12.1, 10.5, 3.6 Hz, 1H), 1.77(m, 2H), 1.66 (m, 2H), 1.41 (m, 2H), 1.29 (m, 5H), 1.17 (s, 3H), 1.14 (m, 1H), 0.91 (t, J = 7.2 Hz, 3H), 0.87 (m, 2H), 0.84 (d, J = 6.4 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.9, 167.1, 152.1, 146.9, 131.1, 128.6, 128.3, 126.0, 125.6, 125.2, 123.1, 118.2, 117.4, 111.7, 76.4, 63.1, 51.5, 49.6, 43.2, 41.1, 39.6, 34.4, 31.2, 28.9, 26.6, 24.7, 21.7, 16.9, 14.1; IR (KBr): ν = 1712 cm^{-1}; HRMS (ESI): m/z calcd for $C_{31}H_{39}NO_4$+Na^+: 512.2771 [M+Na^+]; found: 512.2775; elemental analysis calcd (%) for $C_{31}H_{39}NO_4$: C 76.04, H 8.03, N 2.86; found: C 76.30, H 8.27, N 2.74.

(*R*)-6-Methyl 2-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] 2-(3,4-dimethylpent-3-en-1-yl)-1,2-dihydroquinoline-2,6-dicarboxylate (**29b**). A –78 ºC solution of Me_3SnLi (0.42 mmol) in THF (0.5 mL) was treated with a solution of **28** (85 mg, 0.19 mmol) in THF (1.4 mL). After 1h, 5-bromo-2,3-dimethylpent-2-ene[33] (65 mg, 0.37 mmol) was added. The reaction mixture was stirred for 3 h while slowly warming to room temperature, and then stirred at 25 ºC for 12 h. Work-up as for **15a**, followed by column chromatography purification (SiO_2, EtOAc/hexane 1:10), afforded **29b** as a pale yellow oil in 77% yield (80 mg): ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.64 (dd, J = 8.4, 2.0 Hz, 1H), 7.49 (d, J = 2.0 Hz, 1H), 7.34 (m, 4H), 7.23 (m, 1H), 6.38 (d, J = 8.3 Hz, 1H), 6.37 (d, J = 9.8 Hz, 1H), 5.38 (dd, J = 9.9, 2.0 Hz, 1H), 4.79 (td, J = 10.7, 4.3 Hz, 1H), 3.97 (s, 1H), 3.79 (s, 3H), 2.12 (ddd, J = 12.4, 10.7, 3.5 Hz, 1H), 2.05 (td, J = 12.6, 4.8 Hz, 1H), 1.97 (td, J = 12.7, 4.8 Hz, 1H), 1.83-1.69 (m, 3H), 1.63 (m, 10H), 1.48 (m, 2H), 1.28 (s, 3H), 1.18 (s, 3H), 1.13 (m, 1H), 0.90-0.81 (m, 5H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.7, 167.1, 152.2, 147.0, 131.2, 128.7, 128.3, 126.3, 125.6, 125.2, 124.8, 123.1, 118.3, 117.5, 111.8, 63.2, 51.5, 49.7, 41.2, 39.6, 39.1, 34.4, 31.3, 29.0, 28.6, 26.6, 24.6, 21.7, 20.6, 20.1, 18.5; IR (KBr): ν = 1713 cm^{-1}; HRMS (ESI): m/z calcd for $C_{35}H_{46}NO_4$: 544.3421 [M+H^+]; found: 544.3404; elemental analysis calcd (%) for $C_{35}H_{45}NO_4$: C 77.31, H 8.34, N 2.58; found: C 77.06, H 8.62, N 2.44.

(*R*)-6-Methyl 2-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] 2-phenethyl-1,2-dihydroquinoline-2,6-dicarboxylate (**29c**). A –78 ºC solution of Me_3SnLi (0.88 mmol) in THF (1 mL) was treated with a solution of **28** (180 mg, 0.4 mmol) in THF (3 mL). After 1h, 2-(bromoethyl)benzene (60 μL, 0.44 mmol) was added. The reaction mixture was stirred for 3 h while slowly warming to room temperature, and then stirred at 25 ºC for 12 h. Work-up as for **15a**, followed by column chromatography purification (SiO_2, EtOAc/hexane 1:10), afforded **29c** as a white foam in 70% yield (154 mg, 260 mg): ^{1}H NMR (750 MHz, CD_2Cl_2): δ = 7.68 (dd, J = 8.4, 2.0 Hz, 1H), 7.53 (d, J = 1.9 Hz, 1H), 7.38-7.15 (m, 10H), 6.43 (d, J = 9.9 Hz, 1H), 6.40 (d, J = 8.4 Hz, 1H), 5.44 (dd, J = 9.9, 2.0 Hz, 1H), 4.81 (dt, J = 10.7, 4.3 Hz, 1H), 3.95 (s, 1H), 3.81 (s, 3H), 2.62 (m, 2H), 2.16 (ddd, J = 12.2, 10.5, 3.6 Hz, 1H), 2.02 (ddd, J = 13.6, 12.1, 5.1 Hz, 1H), 1.83-1.72 (m, 3H), 1.66 (m, 1H), 1.46 (m, 1H), 1.28 (s, 3H), 1.18 (s, 3H), 1.15 (m, 1H), 0.89 (m, 2H), 0.85 (d, J = 6.6 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.6, 167.1, 152.3, 146.8, 141.4, 131.2, 128.7, 128.42, 128.36, 128.32, 126.6, 125.9, 125.5, 125.2, 122.7, 118.4, 117.3, 111.8, 76.5, 63.1, 51.5, 49.6, 42.6, 41.1, 39.5, 34.4, 31.2, 30.2, 29.3, 26.5, 24.2, 21.7; ; IR (KBr): ν = 1712 cm^{-1}; HRMS (ESI): m/z calcd for $C_{36}H_{41}NO_4$+Na^+: 574.2928 [M+Na^+]; found: 574.2930; elemental analysis calcd (%) for $C_{36}H_{41}NO_4{\cdot}H_2O$: C 75.89, H 7.61, N 2.46; found: C 75.78, H 7.21, N 2.37. **(*R*)-6-Methyl 2-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] 2-(2-(2-methyl-1,3-dioxolan-2-yl)ethyl)-1,2-dihydroquinoline-2,6-dicarboxylate** (**29d**). A –78 ºC solution of Me_3SnLi (0.42 mmol) in THF (0.5 mL) was treated with a solution of **28** (85 mg, 0.19 mmol) in THF (1.2 mL). After 1h, 2-(2-bromoethyl)-2-methyl-1,3-dioxolane[34] (71 mg, 0.36 mmol) was added, immediately followed by HMPA (0.2 mL). The reaction mixture was stirred for 24 h at –78 ºC. Work-up as for **15a**, followed by column chromatography purification (SiO_2, EtOAc/hexane 1:3), afforded **29d** as a white foam (51mg, 48%): ^{1}H NMR (750 MHz, $CDCl_3$): δ = 7.65 (dd, J = 8.5, 2.0 Hz, 1H), 7.48 (d, J = 2.0 Hz, 1H), 7.39-7.31 (m, 4H), 7.24 (m, 1H), 6.33 (d, J = 9.9 Hz, 1H), 6.28 (d, J = 8.4 Hz, 1H), 5.34 (dd, J = 9.9, 2.0 Hz, 1H), 4.79 (td, J = 10.7, 4.3 Hz, 1H), 3.99-3.89 (m, 4H), 3.82 (s, 3H), 3.64 (s, 1H), 2.11 (ddd, J = 12.3, 10.5, 3.5 Hz, 1H), 1.85-1.73 (m, 3H), 1.65 (m, 3H), 1.59 (m, 1H), 1.45 (m, 1H), 1.31 (s, 3H), 1.27 (s, 3H), 1.17 (s, 3H), 1.12 (m, 1H), 0.84 (m, 2H), 0,83 (d, J = 6.4 Hz, 3H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 172.8, 167.1, 152.3, 146.9, 131.2, 128.7, 128.4, 126.6, 125.6, 125.2, 122.8, 118.3, 117.2, 111.8, 109.7, 64.7, 62.7, 51.5, 49.8, 41.1, 39.6, 35.0, 34.4, 33.3, 31.2, 29.1, 26.6, 24.4, 24.1, 21.7; IR (KBr): ν = 1712 cm^{-1}; HRMS (ESI): m/z calcd for $C_{34}H_{43}NO_6$+Na^+: 584.2983 [M+Na^+]; found: 584.2981.

3-(Methoxycarbonyl)-7-methoxybenzofuran-2-carboxylic acid (31). A 0 ºC solution of dimethyl 7-methoxybenzofuran-2,3-dicarboxylate[27] (**30**, 6.07 g, 23 mmol) in a 1:1 dioxane/H_2O solution (230 mL) was treated with $LiOH{\cdot}H_2O$ (1 g, 24 mmol) and the mixture was stirred for 2 h. The solution was acidified with 6 N HCl, and the white solid obtained was collected, dried and used without further purification (5.64 g, 98%): mp 212-214 ºC (MeOH); ^{1}H NMR (250 MHz, $CDCl_3$): δ = 14.18 (br s, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.34 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 7.9 Hz, 1H), 4.17 (s, 3H), 4.00 (s, 3H); ^{13}C NMR (62.9 MHz, DMSO): δ = 162.8, 159.2, 146.4, 145.3, 142.9, 126.3, 125.8, 117.1, 113.6, 109.7, 56.0, 52.7; IR (KBr): ν = 1760 cm^{-1}; HRMS (ESI): m/z calcd for $C_{12}H_{11}O_6$: 251.0550 [M+H^+]; found: 251.0551; elemental analysis calcd (%) for $C_{12}H_{10}O_6$: C 57.60, H 4.03; found: C 57.25, H 3.99.

3-Methyl 2-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] 7-methoxybenzofuran-2,3-dicarboxylate (32). A solution of **31** (0,94 g, 3.76 mmol), (-)-8-phenylmenthol (872 mg, 3.76 mmol), di-2-pyridyl carbonate (DPC) (850 mg, 3.94 mmol) and DMAP (83 mg, 0.68 mmol) in dry dichloroethane (18 mL) was prepared in a sealed vessel, and refluxed for 1 day. The reaction mixture was cooled to room temperature, H_2O was added to the mixture and the layers were separated. The organic layer was washed with water and brine, dried, and evaporated under reduced pressure. The crude product was purified by flash column chromatography (EtOAc/toluene 1:50) to give **32** (1.47 g, 84%) as a white foam: $[\alpha]^{24}_D$ – 21.6 (c 0.5, MeOH); ^{1}H NMR (250 MHz, CD_2Cl_2): δ = 7.43 (dd, J = 8.0, 0.9 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.23 (m, 2H), 6.99 (m, 3H), 6.66 (m, 1H), 5.12 (td, J = 10.8, 4.5 Hz, 1H), 4.03 (s, 3H), 3.95 (s, 3H), 2.10 (m, 2H), 1.82-1.43 (m, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 1.20 (m, 2H), 0.94 (m, 1H), 0.93 (d, J = 6.4 Hz, 3H); ^{13}C NMR (250 MHz, CD_2Cl_2): δ = 163.2, 158.0, 151.4, 146.6, 146.2, 144.0, 128.1, 127.7, 125.7, 125.1, 118.0, 114.6, 109.4, 76.6, 56.6, 52.6, 51.3, 42.0, 40.2, 35.0, 32.0, 28.1, 27.1, 25.4, 22.1; IR ($CHCl_3$): ν = 1722 cm^{-1}; HRMS (ESI): m/z calcd for $C_{28}H_{32}O_6$+Na^+:

487.2091 [M+Na^+]; found: 487.2091; elemental analysis calcd (%) for $C_{28}H_{32}O_6$: C 72.39, H 6.94; found: C 72.18, H 7.10.

(4a*R*,9b*S*)-9b-Methyl 4a-[(1*R*,2*S*,5*R*)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl] 6-methoxy-1,4,4a,9b-tetrahydrodibenzo[*b*,*d*]furan-4a,9b-dicarboxylate (33). A solution of Me_3SnLi (0.29 mmol) in THF (1,4 mL) was treated with a solution of **32** (65 mg, 0.14 mmol) in THF (1.4 mL) at –78 ºC. After stirring for 1 h, a solution of *cis*-1,4-bis(methylsulfonyloxy)-2-butene[35] (42 mg, 0.17 mmol) in DMF (0.75 mL) was added dropwise, and the reaction mixture was then stirred for 1 day at –55 ºC. The reaction mixture was quenched with deoxygenated pH 5.6 acetate buffer, and partitioned between CH_2Cl_2 and acetate buffer. The aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was washed with water and brine, dried, and concentrated. The crude product was purified by flash column chromatography (EtOAc/tol 1:50) to give **33** (36 mg, 50%) as a pale yellow foam: ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.30 (m, 4H), 7.15 (m, 1H), 6.83 (t, J = 7.8 Hz, 1H), 6.74 (m, 2H), 5.83 (m, 2H), 4.87 (td, J = 10.6, 4.2 Hz, 1H), 3.82 (s, 3H), 3.62 (s, 3H), 2.78 (m, 2H), 2.65 (dd, J = 16.2, 5.8 Hz, 1H), 2.49 (d, J = 16.6 Hz, 1H), 2.05 (m, 2H), 1.47 (m, 2H), 1.36 (s, 3H), 1.26 (s, 3H), 1.24 (m, 1H), 1.07 (dd, J = 23.2, 11.7 Hz, 1H), 0.95 (m, 1H), 0.88 (d, J = 6.3 Hz, 3H), 0.78 (ddd, J = 14.9, 12.5, 2.9 Hz, 1H); ^{13}C NMR (62.9 MHz, CD_2Cl_2): δ = 173.3, 171.4, 151.3, 148.3, 144.8, 131.7, 128.6, 127.8, 126.3, 125.9, 125.8, 122.2, 115.8, 112.8, 94.2, 77.7, 60.8, 56.4, 52.9, 50.9, 41.6, 40.9, 34.9, 34.7, 32.5, 31.9, 31.0, 28.0, 23.1, 22.1; IR (KBr): ν = 1741, 1727 cm^{-1}; elemental analysis calcd (%) for $C_{32}H_{38}O_6$: C 74.11, H 7.39; found: C 74.22, H 7.67.

((4a*R*,9b*R*)-6-Methoxy-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-4a,9b-diyl)dimethanol (34). A suspension of $LiAlH_4$ (60 mg, 1.6 mmol) in THF (1 mL) was treated with a solution of **33** (330 mg, 0.64 mmol) in THF (1.1 mL) at 0 ºC. After being stirred for 3 h at 0 ºC, EtOAc (1 mL) was carefully added, followed by $CHCl_3$, saturated aqueous Na_2CO_3, solid KH_2PO_4 and Na_2SO_4. The resulting suspension was stirred at r.t. for 1h, then filtered over celite and evaporated. The residue was chromatographed through a short column of SiO_2 (4% *i*PrOH-CH_2Cl_2) to give **34** in 75% yield (126 mg) as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.81 (m, 1H), 6.68 (m, 1H), 6.60 (dd, J = 7.4, 1.0 Hz, 1H), 5.78 (m, 2H), 4.05-3.57 (m, 9H), 2.61-2.24 (m, 4H); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 146.9, 143.9, 133.4, 127.2, 126.0, 121.3, 115.1, 111.1, 94.0, 66.5, 65.6, 55.6, 54.2, 32.9, 32.2; HRMS (ESI): m/z calcd for $C_{15}H_{18}O_4$+Na^+: 285.1097 [M+Na^+]; found: 285.1100.

(2*R*,2'*R*)-((4a*R*,9b*R*)-6-methoxy-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-4a,9b-diyl)bis(methylene) bis(2-methoxy-2-phenylacetate) (35). A solution of **34** (61 mg, 0.23 mmol) in 1,2-dichloroethane (0.6 mL) was added to a solution of (*R*)-methoxyphenylacetic acid [(*R*)-MPA] (85 mg, 0.51 mmol), DPC (105 mg, 0.49 mmol) and DMAP (8.5 mg, 0.07 mmol) in 1,2-dichloroethane (0.65 mL). The reaction mixture was stirred for 1 day at 40 ºC. H_2O was added, the layers were separated, and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine, dried, and concentrated. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2) to give **35** (113 mg, 87%) as a colorless foam: $[\alpha]^{24}_D$ – 57.2 (0.5, MeOH); ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.32 (m, 10H), 6.72 (m, 2H), 6.50 (dd, J = 7.2, 1.5 Hz, 1H), 5.63 (m, 2H), 4.76 (s, 1H), 4.68 (s, 1H), 4.36 (d, J = 11.8 Hz, 1H), 4.28 (d, J = 11.8 Hz, 1H), 4.24 (d, J = 11.6 Hz, 1H), 4.19 (d, J = 11.6 Hz, 1H), 3.77 (s, 3H), 3.36 (s, 3H), 3.33 (s, 3H), 2.33 (dd, J = 15.9, 5.6 Hz, 1H), 2.20 (dd, J = 15.7, 5.8 Hz, 1H), 1.98 (m, 1H), 1.89 (m, 1H); ^{13}C NMR (250 MHz, CD_2Cl_2): δ = 170.6, 170.5, 147.5, 144.6, 136.85, 136.83, 132.6, 129.3, 129.2, 129.1, 127.74, 127.67, 126.2, 121.8, 115.7, 112.5, 91.8, 83.0, 82.9, 67.4, 67.2, 57.84, 57.80, 56.2, 52.7, 32.9, 32.0; IR (KBr): ν = 1753 cm^{-1}; elemental analysis calcd (%) for $C_{33}H_{34}O_8$: C 70.95, H 6.13; found: C 70.58, H 6.42.

(2*S*,2'*S*)-((4a*R*,9b*R*)-6-methoxy-1,4,4a,9b-tetrahydrodibenzo[b,d]furan-4a,9b-diyl)bis(methylene)bis(2-methoxy-2-phenylacetate) (36). Following the same procedure as above, but using (*S*)-MPA (91 mg, 0.55 mmol), 65 mg of **34** (0.25 mmol) gave **35** (100 mg, 72 %) as a colorless foam: $[\alpha]^{20}_D$ = +28 (c = 0.5, MeOH); ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.28 (m, 10H), 6.78 (dd, J = 8.0, 7.6 Hz, 1H), 6.72 (dd, J = 8.1, 1.2 Hz, 1H), 6.56 (dd, J = 7.5, 1.2 Hz, 1H), 5.72 (m, 2H), 4.70 (s, 1H), 4.60 (s, 1H), 4.27 (d, J = 11.8 Hz, 1H), 4.18 (d, J = 11.6 Hz, 1H), 4.16 (d, J = 11.6 Hz, 1H), 4.01 (d, J = 11.8 Hz, 1H), 3.77 (s, 3H), 3.34 (s, 3H), 3.33 (s, 3H), 2.41 (dd, J = 15.9, 5.9 Hz, 1H), 2.18 (m, 2H), 2.00 (m, 1H); ^{13}C NMR (250 MHz, CD_2Cl_2): δ = 170.5, 170.3, 147.7, 144.4, 136.73, 136.69, 133.0. 129.2, 129.14, 129.10, 129.07, 127.7, 127.63, 127.58, 126.3, 121.7, 115.7, 112.5, 91.9, 82.9, 67.7, 67.1, 57.8, 56.3, 52.4, 33.5, 32.2; IR (KBr): ν = 1754 cm^{-1}; elemental analysis calcd (%) for $C_{33}H_{34}O_8$: C 70.95, H 6.13; found: C 71.22, H 6.28.

Supporting Information (see footnote on the first page of this article): General experimental methods and copies of the ^{1}H and ^{13}C NMR spectra for all new compounds.

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