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Experimental and Computational Studies into an ATPH-Promoted *exo*-Selective IMDA Reaction: A Short Total Synthesis of Δ^9-THC**

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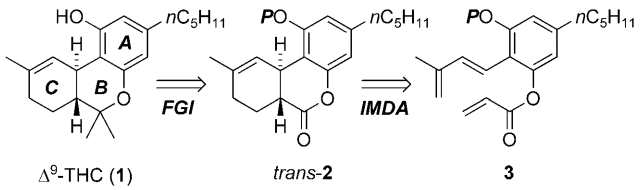
Cannabinoids are tricyclic terpenoid compounds containing a benzopyran moiety. Of the 60 or so known plant-derived cannabinoids, the most well known is (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC; **1**), a natural product isolated from *Cannabis sativa* L. (Indian hemp) and the key psychoactive constituent of marijuana.[1] It exhibits a range of activities including antiemetic, analgesic, and antiglaucoma effects[2] and has been the focus of many synthetic studies.[3,4] In recent times, synthetic interest in these structures has been reinvigorated by the identification of the cannabinoid receptors CB1 and CB2 and their selective binding of THC analogues.[5] Existing synthetic approaches are dominated by strategies involving the construction of ring B through the union of suitably functionalized ring A and ring C building blocks.[3,4] These previous studies have identified two main issues associated with the synthesis of Δ^9-THC: the stereoselective formation of the *trans* ring junction and the unwanted, facile isomerization of its thermodynamically more stable Δ^8-isomer.[3a] Herein, we present a short diastereoselective synthesis of Δ^9-THC (**1**) by a *trans*-selective intramolecular Diels–Alder (IMDA)[6] reaction of an appropriately functionalized, benzo-tethered, ester-linked 1,3,9-decatriene **3** as the key step (Scheme 1). The synthesis is noteworthy for three reasons: 1) it differs from previous approaches in that rings B and C are assembled in one step with concomitant installation of the required Δ^9-alkene (Scheme 2, **3**→**2**), 2) it represents the first total synthesis application of Yamamoto's highly sterically hindered aluminum tris(2,6-diphenylphenoxide) (ATPH) catalyst,[7] and 3) the synthetic work is driven by an understanding of the stereoselectivity of the key IMDA reaction, which in turn is provided through computational analysis. Despite the presence of the cyclohexene ring in many naturally occurring cannabinoids, there are only three published synthetic approaches to cannabinoids employing Diels–Alder reactions: 1) Korte, Dlugosch, and Claussen's approach to *trans*-cannabidiol through an intermolecular cycloaddition,[8] 2) Evans' synthesis of Δ^9-tetrahydrocannabinol through an enantioselective intermolecular cycloaddition,[9] and 3) Inoue's approach to the *cis* isomer of Δ^9-tetrahydrocannabinol through an IMDA reaction.[10]



Scheme 1. Retrosynthetic analysis of Δ^9-THC. ***P*** = protecting/stereodirecting group.

The IMDA precursors **3a–3d**, differing only in the nature of the C12 phenol substituent, were synthesized from olivetol (**4**) through the short sequence depicted in Scheme 2.[11] Protection of the two phenol groups in **4** as methoxymethyl[3d] or ethoxyethyl ethers followed by C6-formylation of the olivetol ring by directed *ortho*-lithiation and trapping with DMF afforded aldehydes **5a** (EE) and **5b** (MOM),[12] respectively. Selective deprotection[12] of one acetal group of **5a** and **5b** afforded monophenols **6a** and **6b**. Methyl ether **6c** was obtained from **6b** through alkylation of the free

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[**] ATPH = aluminum tris(2,6-diphenylphenoxide), IMDA = intramolecular Diels–Alder, THC = tetrahydrocannabinol.

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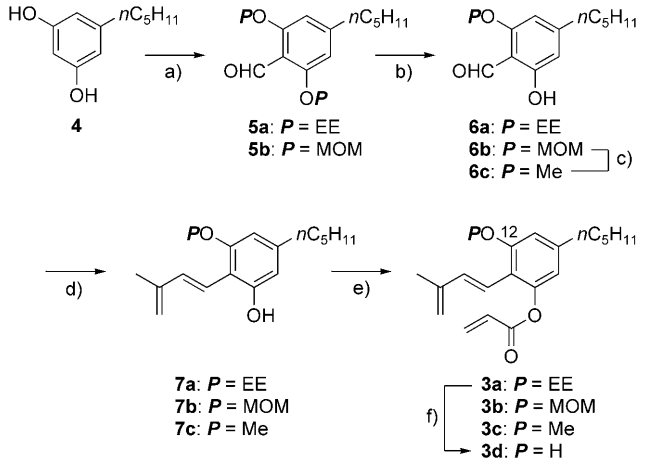
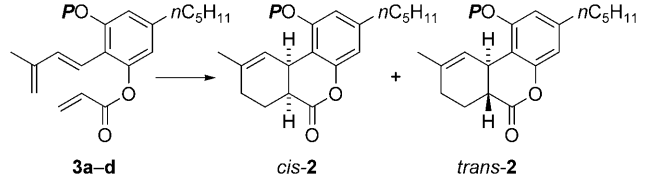


Scheme 2. Synthesis of IMDA precursors **3a–3d**. Reagents and conditions: a) For **5a**: i) EVE (10 equiv), PPTS (0.2 equiv), CH_2Cl_2/DMF, 0 °C, 7 h; ii) *n*BuLi (1.5 equiv), DMF (2.0 equiv), THF, 0 °C, 3 h; for **5b**: i) MOMCl (2.4 equiv), NaH (2.6 equiv), DMF, 0 °C→RT, 3.5 h; ii) *n*BuLi (1.5 equiv), DMF (2.0 equiv), THF, 0 °C, 2 h, **5b**: 83% from **4**; b) for **6a**: SiO_2, CH_2Cl_2, 8.5 h, RT, 67% from **4**; for **6b**: 0.7 M HCl, THF, RT, 3 h, 85%; c) i) MeI (2.0 equiv), Cs_2CO_3 (2.5 equiv), DMF, 35 °C, 2 h; ii) HCl (aq) (1.0 equiv), THF, RT, 3 h, **6c**: 82% from **6b**; d) *n*BuLi (2.4 equiv), $BrPh_3PCHC(CH_3)=CH_2$ (2.5 equiv), THF, −78 °C→RT, 14–17 h, **7a**: 75%; **7b**: 99%; **7c**: 85%; e) DBU (1.4 equiv), $Cl(O)CCH=CH_2$ (1.1 equiv), CH_2Cl_2, −78 °C→RT, 1 h, **3a**: 81%; **3b**: 86%; **3c**: 70%; f) PPTS (0.2 equiv), MeOH, RT, 3.5 h, **3d**: 81%. EVE = ethyl vinyl ether, EE = ethoxyethyl, PPTS = pyridinium *p*-toluenesulfonate, MOM = methoxymethyl.

phenol and subsequent removal of the acetal protecting group. Installation of the *E*-diene was achieved through Wittig olefination of aldehydes **6a–6c** and esterification of the resulting phenols **7a–7c** with acryloyl chloride afforded the trienes **3a–3c**. Removal of the protecting group in **3a** gave the triene phenol **3d**.

The results of thermally promoted IMDA reactions of the four trienes **3a–3d** are summarized in Table 1. Mixtures rich in the undesired *cis*-fused adduct *cis*-**2** (≈3:1 *cis*/*trans*) were generated in all cases, regardless of the C12 substituent.[13]

Table 1. Thermal cyclization of precursors **3a–3d**.[a]



Entry	*P*	Yield[b] [%]	Product distribution *cis*-**2**/*trans*-**2**[c]
1	EE	96	76:24
2	MOM	86	77:23
3	Me	71	73:27
4	H	75	76:24[d]

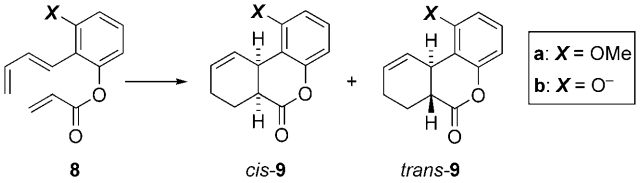
[a] Reagents and conditions: butylated hydroxytoluene (BHT; 5 mol%), PhMe, 110 °C, 4–7 h. [b] Total yield of the isolated product. [c] Kinetic product ratio from crude ^{1}H NMR spectra. [d] The acrylate ester of *cis*-**2d** makes up around 20% of the crude product mixture.

Evidently, the influence of the size of the PO-substituent at C12 has a negligible effect upon IMDA stereoselectivity. The reaction of the phenol substrate **3d** was complicated by concomitant transesterification, a result that highlights the need for phenol masking during the IMDA step.

Frustratingly, attempts to interconvert the *cis* cycloadduct to the *trans* isomer through base-mediated epimerization were also unsuccessful; the *cis* isomer is evidently the thermodynamic product in these reactions. It was clear, therefore, that the successful realization of this synthesis would hinge upon a kinetically controlled *trans*-selective (i.e., *exo*) IMDA reaction. A deeper understanding of the stereocontrolling features of this reaction was needed.

DFT calculations, at the B3LYP/6-31G(d) level of theory,[14] were carried out on a simplified system, **8**, in which the methyl and pentyl spectator substituents are absent, while retaining the 12-methoxy substituent because this group was found to affect the IMDA *cis*/*trans* selectivity.[11] Transition structures (TS) were located for both the *cis* and *trans* IMDA pathways of **8**, uncatalyzed and catalyzed by the Lewis acids $AlCl_3$ and ATPH. Relative enthalpies (H) and Gibbs free energies (G) between the *cis*- and *trans*-TSs for each reaction ($X_{rel\text{-}TS}=X_{cis\text{-}TS}-X_{trans\text{-}TS}$; $X=H$, G) are given in Table 2. Also given in Table 2 are the *cis*/*trans* product ratios, calculated from the $G_{rel\text{-}TS}$ values at 298.15 K.

Table 2. B3LYP/6-31G(d) *cis*/*trans* TS relative enthalpies ($H_{rel\text{-}TS}$)[a] and Gibbs free energies ($G_{rel\text{-}TS}$)[a] for Lewis acid catalyzed and uncatalyzed IMDA reactions and *cis*/*trans* product ratios.

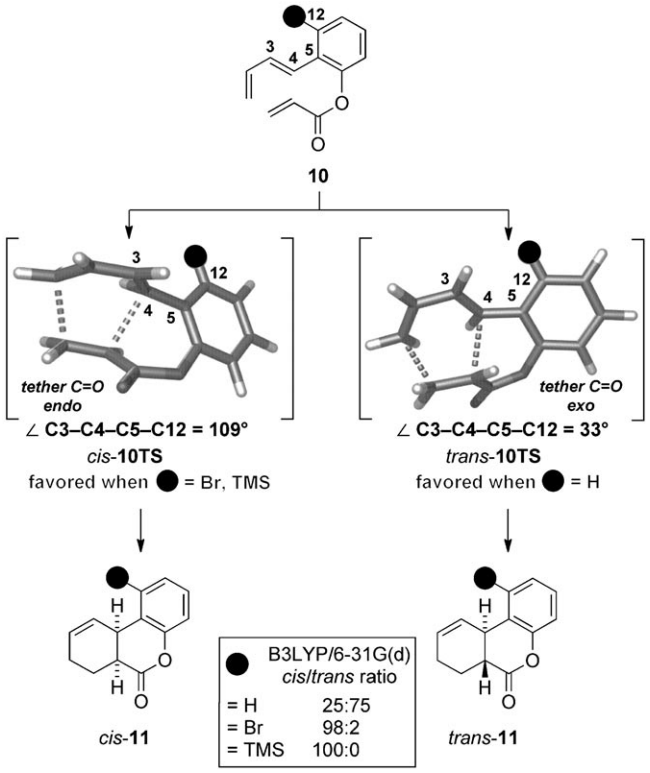


Entry	Reactant	$H_{rel\text{-}TS}$[a]	$G_{rel\text{-}TS}$[a]	*cis*/*trans*[b]
1	**8a**	0.6 (−0.6)[c]	−0.1 (−1.4)[c]	51:49 (63:37)[c]
2	**8a·AlCl$_3$**	−1.3 (−3.0)[c]	−1.5 (−2.4)[c]	65:35 (72:28)[c]
3	**8a·ATPH**	7.0 (7.2)[c,e]	8.3 (7.9)[c,e]	3:97 (4:96)[c,d]
4	**8b**	11.1[e] (5.8)[e]	10.5[e] (5.4)[e]	1:99[e] (10:90)[c,e]

[a] $X_{rel\text{-}TS}=X_{cis\text{-}TS}-X_{trans\text{-}TS}$ ($X=H$ or G), both at 298.15 K and 1 bar pressure. [b] *Cis*/*trans* ratios calculated using $\Delta G^{\ddagger}_{CT}$ values at 298.15 K. [c] Toluene solvent using the polarizable continuum model (PCM) approximation. [d] PCM single-point vibrationless self-consistent field (SCF) energies with gas phase thermal corrections. [e] Calculations at the B3LYP/6-31++G(d,p) level.

Recently, we explored the *cis*/*trans* selectivity in IMDA reactions of a series of hexadienyl acrylates.[15,16] Interestingly, we observed that, whereas the IMDA reaction of the cognate system possessing the ethylene tether ($-CH_2CH_2OC(=O)-$) displays strong *cis* stereoselectivity, the IMDA reactions of the benzo-tethered systems exhibit moderate *trans* selectivity, for example, *cis*/*trans* = 26:74 (Scheme 3).[15]

Our DFT calculations traced the origin of the preference for the *trans* isomer to conjugation effects between the



Scheme 3. In IMDA reactions, unsubstituted benzo-tethered trienes give *trans* selectivity and C12-substituted systems give *cis* selectivity.

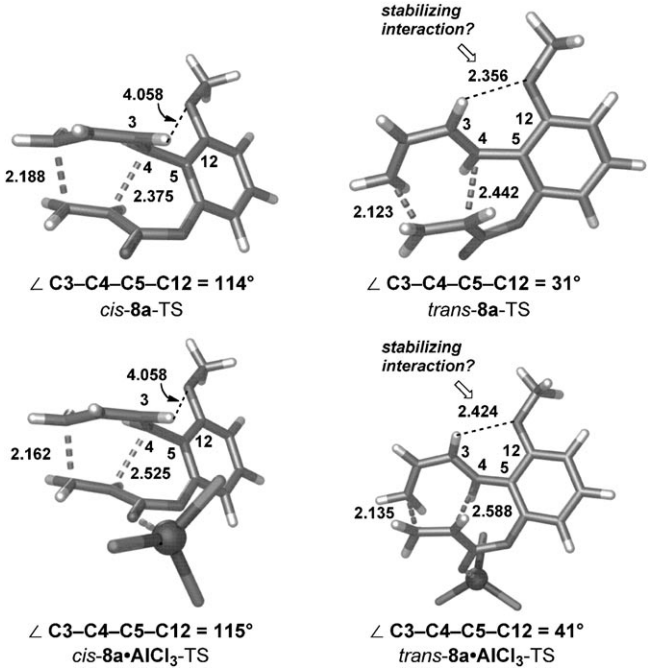


Figure 1. A possible stabilizing C3−H···O interaction leading to decreased IMDA *cis* selectivity. Top: uncomplexed *cis*- and *trans*-IMDA TSs; bottom: $AlCl_3$-complexed *cis*- and *trans*-IMDA TSs.

diene and the aromatic ring of the tether, as reflected in the magnitude of the dihedral angle θ between the diene and the aromatic ring in the *cis*- and *trans*-IMDA TSs for **10**. Whereas the *cis*-TSs suffer nearly perpendicular diene–arene dihedral angles of 103–111°, the *trans*-TSs benefit from substantially increased conjugation between these two groups, with dihedral angles in the 29–33° range (see Scheme 3). These markedly different dihedral angles between the aromatic ring and the C3=C4 double bond in the *cis*- and *trans*-IMDA TSs of **10** suggest that placement of a large group at either C3 or C12 should disfavor the *trans*-TS relative to the *cis*-TS. Both DFT calculations and experimental findings confirmed this expectation: both Br and trimethylsilyl (TMS) substituents at C3 or C12 led to very high *cis*-IMDA selectivities (>95% *cis*) (Scheme 3).[16]

On the basis of these findings, it was expected that the 3-OMe substituent in **8a** should likewise favor formation of the *cis*-IMDA product. The predicted and observed selectivity, stereorandom (gas phase; calculations) or moderately *cis* selectivity (toluene; calculation and experiment), is smaller than might be expected (Table 1, Entry 3; Table 2, Entry 1). Examination of the *trans*-transition-structure geometry, ***trans*-8a-TS**, (Figure 1) reveals the possible existence of a stabilizing (C3)−H···O−(Me) H-bonding interaction. Thus, the distance between the C3−H hydrogen and the methoxy oxygen is only 2.36 Å, which lies close to the (C)−H···O distance determined from X-ray crystal structures of aldehyde–Lewis acid complexes (2.41–2.59 Å).[17]

If this explanation is correct, then the corresponding phenoxide system, **8b**, should display markedly strong *trans*-IMDA selectivity, as a consequence of a stronger stabilizing (C3)−H···O^- interaction. Indeed, B3LYP/6-31++G(d,p) calculations on **8b** confirm this prediction (Table 2): the *trans*-TS is favored over the *cis*-TS by 99:1 (gas phase) and 90:10 (toluene). Carrying out the IMDA reaction on the phenoxide anion derivative of **3d** should, therefore, offer easy access to high yields of *trans* product. Unfortunately, we have been unable to obtain experimental verification of this proposal. All attempts to generate the phenoxide of triene **3d** (Table 1) and effect its IMDA reaction have led to complex mixtures of products.

Common Lewis acids are well known to enhance *endo* selectivity in DA reactions[18] and we find this to be the case for the $AlCl_3$-catalyzed IMDA reaction of **8a** (**8a·$AlCl_3$**, Table 2), the *cis* selectivity rising modestly with respect to the uncatalyzed reaction. However, Yamamoto has shown that ATPH can promote *exo* selectivity in certain DA reactions, a result that was attributed to the difficulty in binding the more sterically encumbered carbonyl oxygen in the *endo* TS.[7] Nevertheless, we have witnessed *endo* stereoselectivity in some ATPH-promoted IMDA reactions[15] and, to our knowledge, no computational study has previously been carried out on ATPH. Notwithstanding the large size of the **8a·ATPH** system, we were able to calculate fully relaxed IMDA *cis*- and *trans*-TSs for **8a·ATPH**. As expected, the calculations predict strong *trans* selectivity of about 96:4 (Table 2). The geometries of ***cis*-8a·ATPH-TS** and ***trans*-8a·ATPH-TS** (Figure 2), regarding how the ATPH Lewis acid wraps around the **8a** donor TS, closely resembles that

with the three trisphenyl ligand arms adopting identical helicity. Inspection of the TS geometries (Figure 2) shows that, whereas there appears to be no destabilizing steric interactions between **8a** and ATPH in *trans*-**8a-TS**, in *cis*-**8a-TS** the C3–H hydrogen lies quite close (2.64 Å) to one of the ATPH phenyl groups (the C3–H hydrogen and the closest aromatic carbon are colored green in Figure 2). The distance between the C3–H hydrogen and the centroid of this aromatic ring is 2.62 Å, which is closer than the distance seen in the methane···benzene complex (≈2.7 Å).[19]

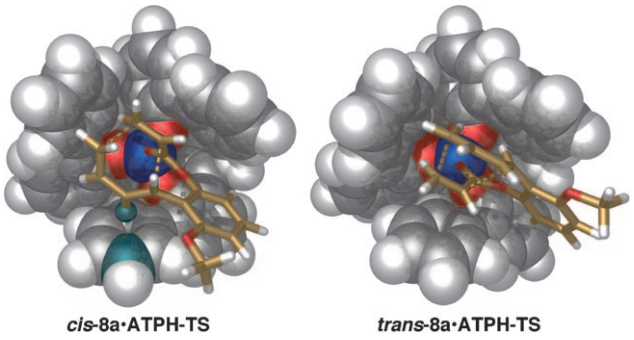
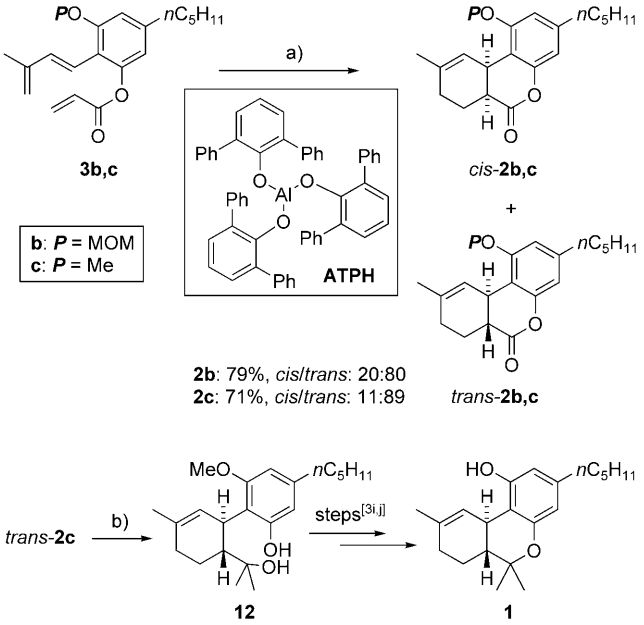


Figure 2. *Cis*- and *trans*-IMDA transition structures of triene **8a** complexed by ATPH. Note the destabilizing steric interaction in the *cis*-TS (green atoms).

Experimentally, ATPH promoted a dramatic reversal in IMDA diastereoselectivity, favoring the *trans* isomer in two of the four triene substrates, namely the MOM ether and the methyl ether systems **3b** and **3c** (Scheme 4). With a successful approach to the *trans* cycloadduct in hand, all that remained was the elaboration into the natural product. The formal total synthesis[20] of Δ^9-THC (**1**) was completed by the reaction of *trans*-**2c** with methyl magnesium chloride, to afford hydroxy phenol **12**. This compound has previously been converted into **1** in two steps (Scheme 4).[3i,j]

In summary, a short synthetic route to Δ^9-THC employing a *trans*-selective IMDA reaction has been achieved. Thermal reactions of trienes **2** gave cycloadduct mixtures **3** rich in the *cis* diastereomer—but less so than was expected. Computational studies point to a CH···O hydrogen bond stabilizing the TS leading to the *trans* isomer. The inherent *cis* stereoselectivity of the uncatalyzed IMDA reaction was overridden through promotion with ATPH, in the first application of this catalyst in total synthesis. Computational studies indicate a destabilizing CH···arene interaction between the substrate and catalyst in the TS leading to the *cis* isomer. These insights promote the application of this remarkable and under-utilized catalyst in synthesis.



Scheme 4. ATPH-catalyzed IMDA cyclization of **3b** and **3c** and the formal total synthesis of Δ^9-THC. Reagents and conditions: a) ATPH, CH_2Cl_2, −18→0 °C, 8 h, **2b**: 79 %, **2c**: 71 %; b) MeMgCl (10 equiv), Et_2O, 35 °C, 30 min, 96 %.

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Keywords: cannabinoids · density functional calculations · diastereoselectivity · Diels–Alder reactions · total synthesis

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[13] The relative configuration of IMDA adduct **2** was elucidated by single crystal X-ray analysis of *cis*-**2c** obtained from the deprotection of **2a**. See the Supporting Information for details. CCDC-772674 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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