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Divergent Photocyclization/1,4-Sigmatropic Rearrangements for the Synthesis of Sesquiterpenoid Derivatives

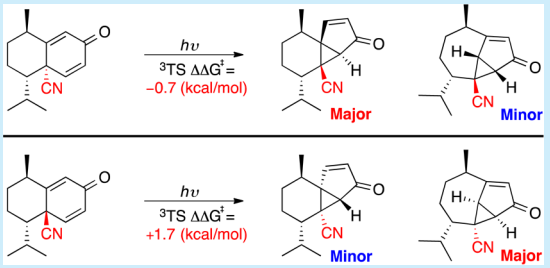
Evgueni Gorobets,[†] Norman E. Wong,[†] Robert S. Paton,[‡] and Darren J. Derksen*[,†]

[†]Department of Chemistry, University of Calgary, 2500 University Drive NW, Calgary, Alberta Canada T2N 1N4

[‡]Chemistry Research Laboratory, Oxford University, Mansfield Road, Oxford OX1 3TA, U.K.

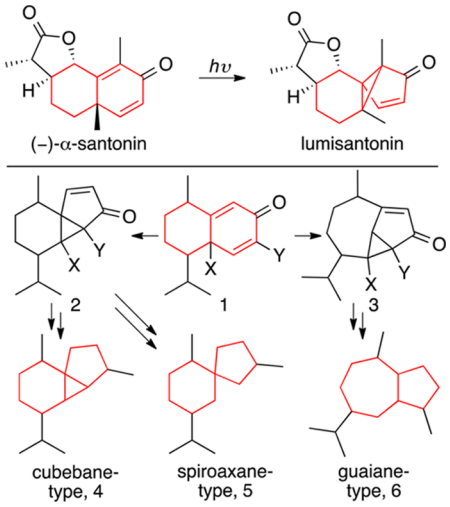
Supporting Information

ABSTRACT: Combined experimental and computational efforts have demonstrated the utility of divergent photocyclization/1,4-sigmatropic rearrangement reactions for developing a general strategy toward the synthesis of cubebane-, spiroaxane-, and guaiane-type sesquiterpenes and related analogues. The configuration of the bridgehead substituent, the choice of solvent, and the wavelength of irradiation all impact diastereoselectivity in this tandem reaction process.



Based on our interest in identifying natural products that interact with transient receptor potential channels,[1] we required alternative strategies to access cubebane, guaiane, and spiroaxane sesquiterpene frameworks for the synthesis of analogues (Scheme 1, **4**–**6**). Inspired by the well-known rearrangement of α-santonin to lumisantonin and related applications in synthesis,[2] we aimed to establish a general strategy to access the functionalized tricyclic cores (**2**, **3**) using the tandem photocyclization/1,4-sigmatropic rearrangement sequence. The [1,4]-sigmatropic rearrangement (1,4-SR) reaction has intrigued synthetic chemists for decades but has been relatively underutilized in organic synthesis compared to other rearrangement reactions.[3] The rich chemistry of divinyl ketones is well-known from elegant work on Nazarov chemistry to generate complex cyclopentanones,[4] and the related acid-catalyzed dienone−phenol rearrangement has been investigated extensively.[5] Oxyallyl cation intermediates generated from irradiation of monocyclic dienones have been used to concisely generate complex polycyclic frameworks and have been examined computationally.[6] Central to our synthetic strategy is an understanding of the impact that existing stereocenters have on the regio- and stereochemical outcome of the tandem reaction. The bridgehead substituent (Scheme 1, **1**-**X**) plays a key role in the rearrangement of fused ring systems by dictating the stereochemical outcome of the initial photocyclization reaction. In santonin-derived syntheses, a methyl substituent is utilized at the bridgehead position imposing severe limitations on subsequent functionalization.[2] Balancing substituent stability with the ability to be removed under reductive reaction conditions, we selected the nitrile moiety as a versatile bridgehead functional group. From tetrahydrocarvone **7**, the nitrile moiety was introduced using tosyl cyanide and LDA (**8**), followed by annulation using methyl vinyl ketone and catalytic sodium methoxide (**9**/**10**, Scheme 2). Dehydration of **9** to form the α,β-unsaturated ketone was followed by formation of dienone **11** via halogenation and elimination (85% over three steps). In order to obtain gram quantities of **10**, a revised synthetic strategy was also devised from (*R*)-carvone[7,8] (see the Supporting Information for details).Conversion of **10** to the divinylketone **12** occurred in a similar fashion; however, Saegusa oxidation was required as the analogous halogen elimination strategy used for **9** gave low yields of the desired product (5%). With the key precursors in hand, the central

Scheme 1. (Top) Photomediated Rearrangement of α-Santonin. (Bottom) Retrosynthesis for the Divergent Syntheses of Sesquiterpene Frameworks Using Tandem Reactions



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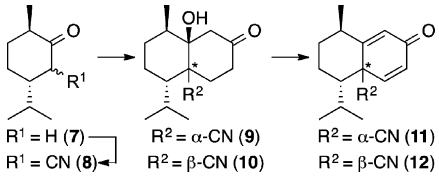
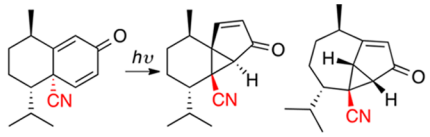
Scheme 2[a]



[a]Key: (a) *p*-Tol-SO_2CN, LDA, −78 °C, 85%; (b) NaOMe, methyl vinyl ketone, 64% (5.3:1); (c) (i) TFAA, DIPEA, 93%, (ii) TMSOTf, NEt_3, (iii) $Pd(OAc)_2$, 77% or NBS; $LiCO_3$, 85%.

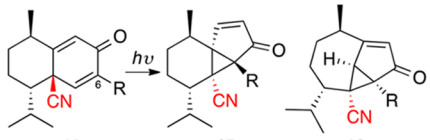
photorearrangement/1,4-SR sequence could be explored. Irradiation conditions of **11** and **12** were evaluated by varying the solvents and wavelengths of light (monitoring by ^{1}H NMR spectroscopy). Exposure of **11** in benzene to visible light (400−700 nm) provided low conversion and selectivity to **13**:**14**, which improved slightly when UV-A (315−400 nm) or UV-B light (280−315 nm, Scheme 3, entries 1−3) was used. To minimize the amount of degradation byproducts observed on an increased scale, it was necessary to recycle starting material through the reaction conditions (entries 4 and 5). Changing the solvent to acetonitrile had a marked effect of reaction rate and selectivity. A consistent improvement in the conversion of starting material was observed when the wavelength was increased from visible to UV−C light (UV-C: 235−280 nm; Scheme 3, entries 6−10). Contrary to the reactivity of **11**, the tandem reaction of **12** in benzene was highly selective for **16** regardless of the wavelength of light used (entries 11−13). The reaction selectivity of **12**−**16** was essentially unaffected by C6 substituents as incorporation of a halogen produced the respective bromo derivative[9] of **16** (entries 14 and 15). The 6-methyl and 6-cyano substituents formed the respective derivatives of **16**, containing adjacent chiral quaternary centers, in good yield using visible light (entries 16 and 17). Upon switching the solvent to acetonitrile, **15** could be observed in the course of the irradiation with visible light; however, the ratio of **15**/**16** decreased until only **16** remained after full conversion of starting material (entries 18−20). Similar results were obtained when UV-A and UV-B light were used, requiring significantly shorter reaction times (entries 21−23), while UV-C was optimal for obtaining **15** (entries 24−26). Extending reaction times using UV-C light led to complex mixtures of degradation byproducts. Although substrate configuration plays a major role in the outcome of the tandem reaction process, the choice of solvent and wavelength of irradiation have a significant impact on the regioselectivity observed in the resulting products. A similar dependence of wavelength on product selectivity in photochemical reactions has been previously reported.[10] After the tandem rearrangement sequence, the choice of retention or fissure of the cyclopropane moiety determines the natural product framework to be obtained. Reduction of **13** was accomplished by hydrogenation with Pd/C to produce **17** (Scheme 4). Generation of the spirocycle **18** occurred by reductive ring-opening of **17** using sodium napthalide at low temperature.[11] Following literature precedent for decyanation reactions, ketone **18** was protected as the cyclic acetal before reaction with potassium/HMPA.[12] Removal of the acetal under mildly acidic conditions generated the spiroaxane-like compound **20**. Compound **17** can also be directly protected to form a cyclic acetal, and exposure to dissolving metal conditions followed by acid treatment completes the decyanation reaction to maintain the cube-

Scheme 3. Optimization of Irradiation Conditions (See the SI for Details)



11 **13** **14**

entry	light[a]	time[b] (h)	13:14[c] ([13+14]:11)	isolated yield (%)[d]
1[e,f]	visible	24	2:1 (5:95)	--
2[e,f]	UV-A	0.5	2:1 (24:76)	--
3[e,f]	UV-B	2	3:1 (20:80)	--
4[e,g]	UV-B	4	3:1	56
5[e,g]	UV-B	4	3:1	13[h]
6[f,i]	visible	2	4:1 (5:95)	--
7[f,i]	UV-A	2	3:1 (26:74)	--
8[f,i]	UV-B	2	3:1 (46:54)	--
9[f,i]	UV-C	0.7	9:1 (98:2)	--
10[i,j]	UV-C	2	9:1	81



12 **15** **16**

entry	R	light[a]	time[b] (h)	15:16[c] ([15+16]:12)	isolated yield (%)[d]
11[e,f]	H	visible	100	0:1	89
12[e,f]	H	UV-A	2	0:1 (90:10)	--
13[e,f]	H	UV-B	2	0:1 (38:62)	--
14[e,f]	Br	visible	100	0:1 (16:84)[k]	--
15[e,f]	Br	UV-A	3	0:1	32[k]
16[e,f]	CH_3	visible	100	0:1	89
17[e,f]	CN	visible	100	0:1	88
18[f,i]	H	visible	20	1:9 (53:47)	--
19[f,i]	H	visible	44	1:19 (75:25)	--
20[f,i]	H	visible	80	0:1 (99:1)	--
21[f,i]	H	UV-A	3	0:1 (100:0)	--
22[f,i]	H	UV-A	9	0:1	79
23[f,i]	H	UV-B	2	1:10 (65:35)	--
24[f,i]	H	UV-C	0.8	1:4.5 (93:7)	--
25[i,j]	H	UV-C	3	1:4.5	47
26[i,j]	H	UV-C	3	1:4.5	14[h]

[a]Type of light bulb used. [b]Hours irradiated. [c]Ratio based on crude ^{1}H NMR spectra. No ratio indicates maximum conversion to isolated product. [d]Yield of major product unless indicated. [e]Benzene solvent. [f]5−70 mg scale. [g]480 mg scale, yields based on two recycles. [h]Yield of minor product. [i]Acetonitrile solvent. [j]150−180 mg scale. [k]Low conversion with extensive product degradation observed.

bane-like ring system of known compound **19**.[13] Utilizing an identical strategy, rearrangement product **15** was hydrogenated to produce **21** in high yield. Acetal formation, decyanation, and acid treatment to ketone **22** then allowed clean conversion to the natural product cubebol (**23**) by treatment with MeLi and $CeCl_3$.[13,14]

Hydrogenation of **16** produced tricyclic compound **24** (Scheme 5). Reductive ring opening using sodium naphthalide generated **25** as a separable but inconsequential mixture of

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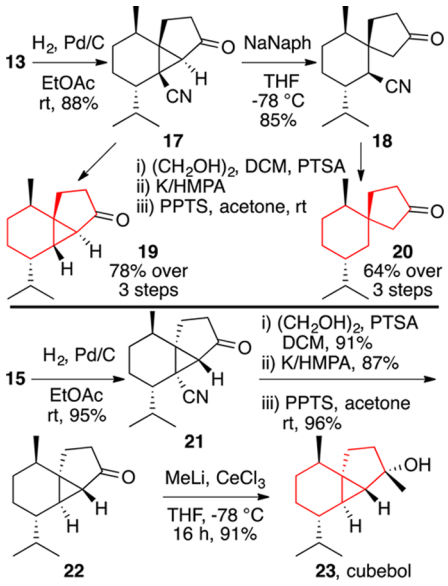
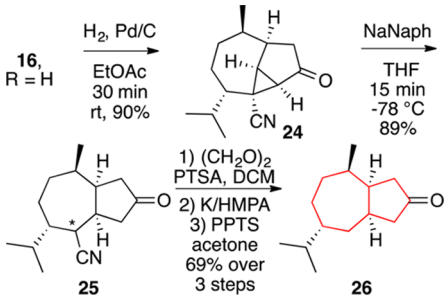
Scheme 4. (Top) Reduction and Ring Opening of 13 Followed by Reductive Decyanation To Generate Spiroaxane- or Cubebane-Type Frameworks. (Bottom) Synthesis of Cubebol



Scheme 5. Reduction and Ring Opening of 16 Followed by Decyanation To Form Guaiane-Type Scaffold



diastereomers (85:15), and a three-step sequence produced the decyanated, guaiane-type compound **26**. The decyanation of tertiary nitrile **24** occurs using conditions analogous to those used for **17** and **21** (see the SI for details).

Given the utility of tricyclic frameworks **13**−**16** as intermediates in complex molecule synthesis, we investigated the competing mechanisms computationally (Figure 1).[15] The M06-2X exchange-correlation functional was used for all geometry optimizations and the Karlsruhe def2-SZVP basis set for all elements. Single-point energetics were further refined with a larger def2-TZVP basis set and implicit SMD description of acetonitrile.[16] The uM06-2X functional has been used previously by Houk and co-workers to describe the triplet PES of the di-π-methane rearrangement of dibenzobarrelenes and gives results comparable to those of multiconfigurational (MCSCF) calculations.[17] In accordance with Zimmerman's seminal experimental findings,[18] C3−C5 bond formation in triplet states of cyclohexadienones **11** and **12** is facile (barriers of 3.6 and 6.1 kcal/mol, respectively). Recent MCSCF computations on the santonin−lumisantonin rearrangement show that intersystem crossing (ISC) to the singlet state can occur either at this stage or following subsequent C−C cleavage.[19] The formation of Woodward−Hoffmann disallowed products **14** and **16** is inconsistent with singlet ground-state reactivity (i.e., a Zimmerman type A zwitterion) and suggests ISC occurs after C−C cleavage. Therefore, assuming that cyclopropyl ring-opening takes place in the triplet state, we obtained competing transition structures (TSs) in which the cleavage of either C−C bond takes place to give the two product skeletons. The activation barriers for these TSs are all feasible and, most importantly, are consistent with the observed switch in product selectivity obtained from **11** and **12**: the computed selectivity is 3.3:1 ($\Delta\Delta G^{\ddagger}$ 0.7 kcal/mol) in favor of cubebane **13** and 1:12.6 ($\Delta\Delta G^{\ddagger}$ 1.7 kcal/mol) in favor of guaiane **16**.[20] This computed switch in selectivity was independent of the level of theory used: uwB97XD, uB3LYP-D3(BJ), and uB2-PLYP single-point energies for the TSs with the def2-TZVP basis set all favor the formation of cubebane **13** (by 0.2−0.7 kcal/mol) and guaiane **16** (by 1.6−1.7 kcal/mol). The triplet pathway for each diastereomer is thus predicted to occur with opposite selectivity. Nevertheless, excited and ground singlet-state reactivity is also plausible for both diastereomers. The cyclopropane-opening TSs (A-B, A-C, D-E, D-F) lead to triplet diradical intermediates which, following

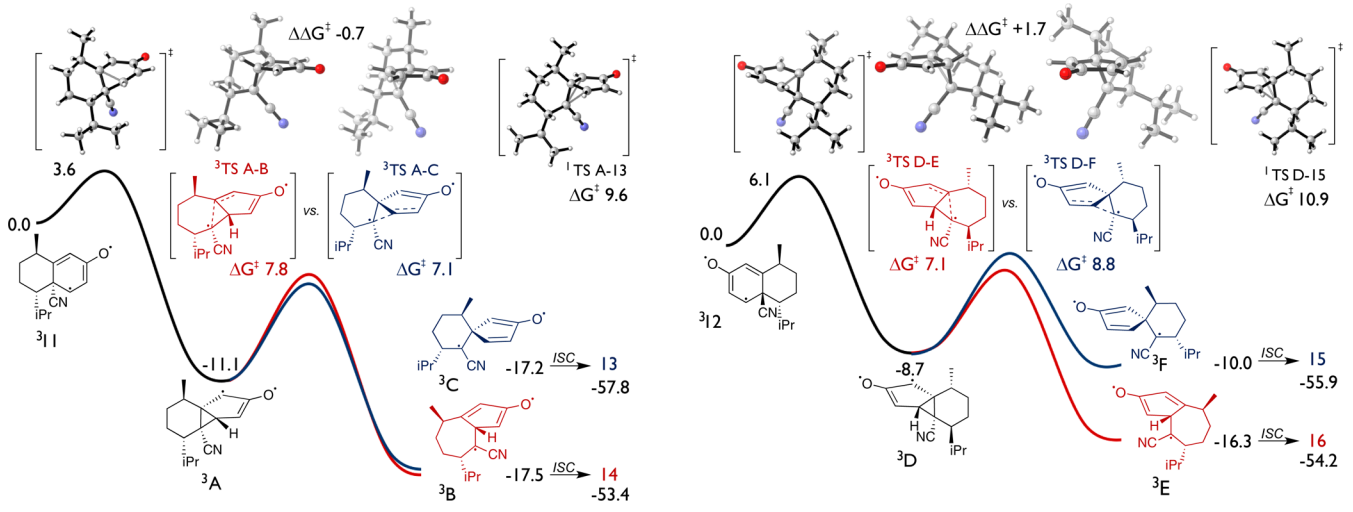


Figure 1. Rearrangements of **11** and **12**. SMD-uM062X/def2-TZVP//uM062X/def2-SVP relative Gibbs energies (kcal/mol).

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ISC, were found to evolve barrierlessly to singlet products. Alternative diastereomers to those observed experimentally were investigated for these stepwise rearrangements, although in every case these were substantially disfavored by more than 25 kcal/mol. In addition, a singlet, concerted [1,4]-sigmatropic rearrangement was also found for the formation of cubebane product in each case: although this pathway could take place if ISC occurs earlier, these TSs were found to be less stable than the triplet TSs discussed above. Our combined experimental and computational efforts indicate that cyclohexyl substituents exert a controlling steric influence on product selectivity. In the favored TS A−C, the cyclohexyl ring is half-chair-shaped with pseudoequatorial Me and ^{i}Pr groups; in the disfavored TS D−F, a twist-boat conformation results in which there is an unfavorably small contact (2.17 Å) between the cyclopentadienyl and ^{i}Pr substituents (see the SI). We speculate that the increased formation of cubebane-type products at lower wavelengths may occur due to C−C formation in an excited singlet state and that a singlet [1,4]-rearrangement could also bypass the involvement of the triplet pathway. The tandem photocyclization/1,4-sigmatropic rearrangement strategy is a viable method to access densely functionalized polycyclic frameworks found in cubebane-, spiroaxane-, and guaiane-type sesquiterpenes. Computational evidence is consistent with singlet and triplet mechanisms competing to form reaction products depending on conformational effects of the substituents. With new insights gained from the tandem cyclization rearrangements of **11** and **12**, we are focusing our efforts on developing novel methods to further control selectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03635.

Experimental procedures, computational details, Cartesian coordinates, absolute energies, and UV−vis spectra (PDF)

^{1}H and ^{13}C spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: dderksen@ucalgary.ca.

ORCID

Robert S. Paton: 0000-0002-0104-4166

Darren J. Derksen: 0000-0002-5945-6921

Notes

The authors declare no competing financial interest.

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