PAs, which are close to the values calculated for this site. In the case of 7 an equal basic strength is forecasted for the carbonyl oxygen and for the pyridine nitrogen by either method of calculation. However, both methods fail to reproduce accurately the experimental PA. This lack of fit precludes any reasonable assignment of the preferred site of protonation. The amino nitrogen of nornicotine (1) seems to be the favored site of protonation (about 3 kcal·mol^{-1}, stronger than the pyridine nitrogen) when one compare the $PA_{AM1corr}$ and PA_{exp}. However the empirical substituent effect model gives a difference of only 1 kcal·mol^{-1} in favor of the amino nitrogen. Though the gas-phase basicity order of the two sites seems to be established, we maintain a reserve on the quantitative difference. The case of nicotine (2) is more clear-cut. The amino nitrogen appears as more basic than the pyridine nitrogen by at least 4 kcal·mol^{-1}. This is confirmed by the agreement between the PAs calculated for the amino site and the experimental PA.

Conclusion

The two basic sites present in nicotines 1 and 2, and in nicotinamides 6 and 7 are of close strength in the gas phase. Comparisons between experimental PAs and the results of AM1 calculations and empirical substituent effect estimations enabled us to assign the favored site of protonation for all the compounds included in this study, except in the case of *N,N*-diethylnicotinamide (7). For this molecule, calculated PAs obtained for each potential site of protonation are very close. This is not the case for nicotinamide (6) for which the preferred site of protonation is undoubtly the pyridine nitrogen. The same conclusion applies for the other carbonyl derivatives 3–5. On the contrary, nornicotine (1) and nicotine (2) appear to be preferentially protonated on the five membered ring amino nitrogen in the gas phase. The relevance of the present results to the behavior of bases 1–7 in solution will be discussed in a future paper.

Acknowledgment. We wish to thank Prs. O. Exner and R. W. Taft for their valuable comments.

Registry No. 1, 494-97-3; 1·H$^+$, 133777-61-4; 2, 54-11-5; 2·H$^+$, 19527-02-7; 3, 350-03-8; 3·H$^+$, 17548-86-6; 4, 5424-19-1; 4·H$^+$, 17548-92-4; 5, 93-60-7; 5·H$^+$, 76137-41-2; 6, 98-92-0; 6·H$^+$, 38719-50-5; 7, 59-26-7; 7·H$^+$, 133777-62-5.

Supplementary Material Available: Atomic coordinates, bond lengths, and bond and dihedral angles calculated by the AM1 method are given for molecules 1–7, for the protonated structures indicated in Table II, and for *N,N*-diethylacetamide (DEAC) and *N,N*-dimethylbenzamide (DMBZ) (neutral molecules and carbonyl protonated) (46 pages). Ordering information is given on any current masthead page.

Intramolecular Cyclopropanation–Ring Fragmentation Leading to Spirocyclic Ring Construction: A Stereoselective Synthesis of β-Chamigrene

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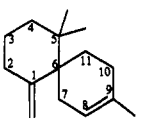
The transannular cyclopropanation of a keto carbene generated by $Rh_2(OAc)_4$ catalysis on a bicyclic dihydropyran nucleus provided a key oxatricyclic ketone intermediate for the synthesis of the [6.6] spirocyclic ring construction. Selective fragmentation of the cyclopropane followed by hydrolytic cleavage of the C–O bond provided the spirocyclic skeleton. Functional group manipulations to adjust oxidation states led to a total synthesis of (±)-β-chamigrene in 14 steps without the use of protection/deprotection schemes.

Introduction

Several years ago we described methodology for intramolecular cyclopropanation of dihydropyrans to form strained oxatricyclic ketones.[1] The cyclopropanation reaction was mediated by a $Rh_2(OAc)_4$-catalyzed decomposition of an α-diazo ketone. This reaction proceeded in high yield and proved to be generally reliable for the formation of small- and medium-sized tricyclic compounds. Regioselective ring fragmentation of the cyclopropane produced oxabicyclic ketones and eventually 6-, 7-, 8-, or 9-membered ring carbocycles as summarized in Scheme I. We wish to report a total synthesis of the spirocyclic sesquiterpene (±)-β-chamigrene (1) by this cyclopropanation–fragmentation strategy using a more highly substituted dihydropyran.



(±)- β-chamigrene 1

β-Chamigrene was first isolated in 1967 from the leaves of *Chamaecyparis taiwanensis*.[2] This rather simple molecule presents the synthetic challenge of constructing two contiguous quaternary carbon centers. Earlier syntheses successfully addressed this problem, using different strategies.[3a-c] We benefitted from these published

(1) Adams, J.; Frenett, R.; Belley, M.; Chibante, F.; Springer, J. P. *J. Am. Chem. Soc.* **1987**, *109*, 5432.

(2) Ito, S.; Endo, K.; Yoshida, T.; Yatagai, M.; Kodama, M. *J. Chem. Soc., Chem. Commun.* **1967**, 186.

(3) (a) Tanaka, A.; Uda, H.; Yoshikoshi, A. *J. Chem. Soc., Chem. Commun.* **1967**, 188. (b) Ireland, R. E.; Dow, W. C.; Godfrey, J. D.; Thaisvrivongs, S. *J. Org. Chem.* **1984**, *46*, 1001. (c) Martin, J. D.; Perez, C.; Ravels, J. L. *J. Am. Chem. Soc.* **1986**, *108*, 7801.

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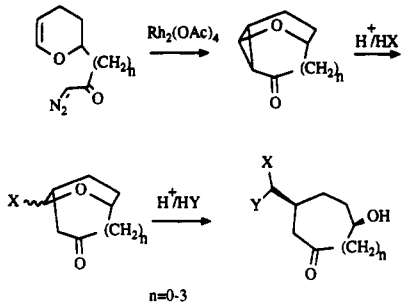
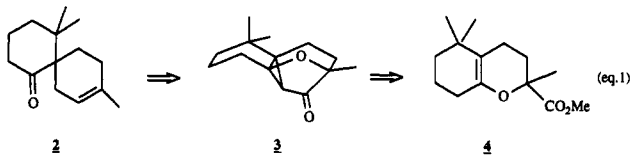
Scheme I



accounts in the final stage of the synthesis by converting the known spiro enone **2** by Wittig methylenation to (±)-β-chamigrene.[3a]



2 **3** **4**

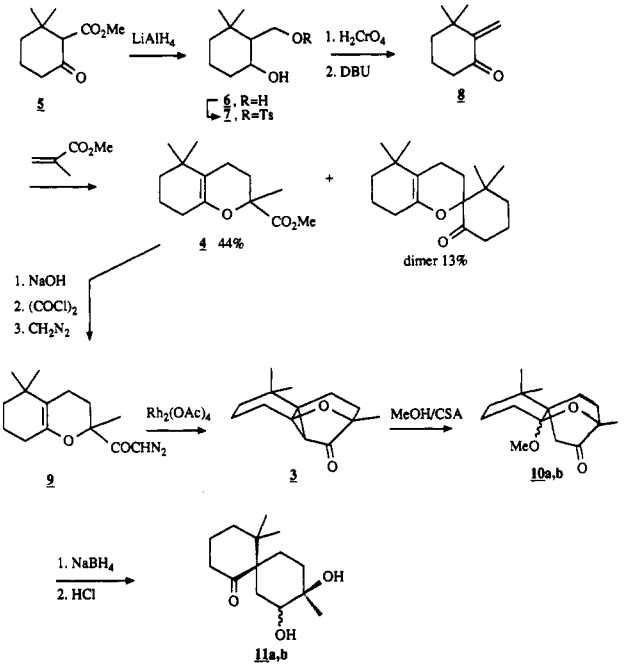
Results and Discussion

The retrosynthetic analysis using the general approach outlined in Scheme I requires tetrahydrochroman **4** as a precursor (eq 1). Although **4** is unknown, literature precedent suggested that it could be prepared via a Diels–Alder reaction of 3,3-dimethyl-2-methylenecyclohexanone (**8**) and methyl methacrylate.[3b] Thus enone **8** was derived from the known keto ester **5** in four steps. Keto ester **5** was prepared in a large quantity according to the procedure of White et al.[4] Exhaustive reduction of keto ester **5** afforded the diols **6** in 77% yield. The primary alcohols could be selectively converted to monotosylates **7** in 78% yield, after which Jones oxidation afforded the keto tosylate intermediate in near quantitative yield. This material was treated immediately with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to effect the elimination of the tosylate and afforded a near quantitative yield of enone **8**. The enone is relatively unstable and dimerizes on standing. This material was carried directly to the next step.

In an attempt to shorten the number of synthetic steps, we attempted the rearrangement of 1-*tert*-butylcyclopentanol over $FeCl_3/SiO_2$ described by Fadel and Salaun, to produce 1,2,2-trimethylcyclohexene.[5] Disappointingly, our yields were not satisfactory. The approach was further plagued with difficulties since the singlet oxygen ene reaction with Ac_2O/Na_2CO_3 described by Ireland to produce the enone **8** also failed to provide acceptable yields.[3b] Returning to keto ester **5**, $LiAlH_4$ reduction to produce the allylic alcohol 3,3-dimethyl-2-methylenecyclohexanol, a method described by Heathcock, was attempted. Unfortunately we were unable to control the reduction to provide the desired allylic alcohol.[6]

Ireland and co-workers[3b] reported a similar Diels–Alder reaction of a related α-methylenecycloheptanone with methyl methacrylate. Their procedure was employed and a modest 44% yield of the desired dihydropyran **4** was realized, together with the dimerized enone (13% yield).[7]

Scheme II



5 **8** **9** **3** **10a,b** **11a,b**

With dihydropyran ester **4** in hand, it was a simple matter to convert this material to diazo ketone **9**. Caution was employed in exposing the dihydropyran to acidic media to avoid acid-catalyzed polymerization, which occurs readily with dihydropyran-2-carboxylic acid. Saponification of the ester with 1 equiv of NaOH and isolation of the sodium salt, followed by conversion to the acid chloride under neutral conditions with oxalyl chloride and treatment with excess CH_2N_2 afforded diazo ketone **9** in 62% overall yield. The cyclopropanation reaction proceeded without incident, using $Rh_2(OAc)_4$ catalysis to generate the carbene, and cyclopropane **3** was produced in quantitative yield.[9] To this point, the strategy for creating two contiguous quaternary centers was successful. It remained to effect a sequential two-bond fragmentation—the C–C cyclopropyl ring and the C–O bridge—to realize the desired [6.6] spirocyclic system.

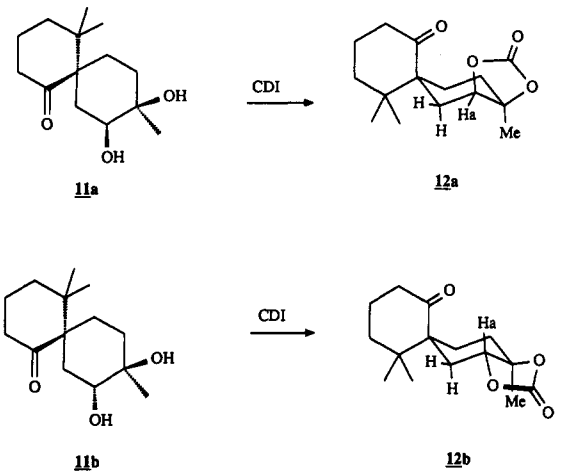
Regiospecific cleavage of the cyclopropane ring was easily achieved through an acid-catalyzed solvolysis of **3** using camphorsulfonic acid in MeOH to provide a ~1:1 mixture of acetals **10a,b** in 91% yield. The driving force for the reaction is the relief of ring strain through the formation of an oxonium ion–enolic intermediate. The lack of stereochemical control in the methanolysis is of no consequence since this carbon center will eventually be converted to a corresponding carbonyl group.

At this stage we sought to effect a reduction of the ketone to a methylene unit, followed by hydrolysis to provide a known keto alcohol.[3a] All attempts at Wolff–Kishner reductions, including milder modifications, failed.[10] Although the hydrazone, or tosylhydrazone, could be formed, attempts at reduction led to decomposition. The reasons for this instability under basic conditions are not understood.

We eventually opted for the alternate strategy shown in Scheme II. First ketones **10a,b** were reduced by using standard $NaBH_4$/MeOH conditions, affording a mixture of four diastereomeric alcohols, followed by an aqueous

(4) White, J. D.; Skeen, R. W.; Trammel, G. L. *J. Org. Chem.* **1985**, *50*, 1939.
(5) Fadel, A.; Salaun, J. *Tetrahedron* **1985**, *41*, 413.
(6) Ellis, J. E.; Dutcher, J. S.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 2670.
(7) As in the Ireland approach to β-chamigrene, the spirocyclic system might also be realized by using a Lewis acid catalyzed Diels–Alder reaction of enone **6** with isoprene. The limitation of this approach is that only racemic (±)-β-chamigrene can be formed since no diastereomeric control of the Diels–Alder reaction is possible.
(8) For other examples of cyclopropanation of enol esters, see: Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.
(9) Kabalka, G. W.; Summers, S. T. *J. Org. Chem.* **1981**, *46*, 1217.
(10) Sarma, J. C.; Barua, N. C.; Sharma, R. P.; Barua, J. N. *Tetrahedron* **1983**, *39*, 2843.

Scheme III



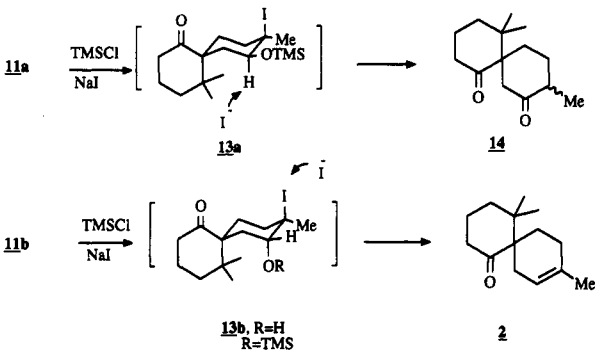
hydrolysis to provide a 1.3:1 mixture of keto diols **11a,b** in 82% overall yield. These diols could be conveniently separated by chromatography, and their structures were assigned upon derivatization to their corresponding cyclic carbonates, using 1,1′-carbonyldiimidazole/(*N*,*N*-dimethylamino)pyridine (CDI/DMAP) in dimethylformamide (Scheme III).

The cis stereochemistry was assigned to **12a**, derived from **11a**, based on the two small ^1H NMR coupling constants of the methine (Ha): J_1 = 3.5 Hz and J_2 = 5.3 Hz, indicating two equatorial couplings. The trans stereochemistry for **12b** was confirmed for the analogous methine (Ha): J_1 = 13.5 Hz and J_2 = 3.5 Hz, diagnostic of an axial and an equatorial relationship to the adjacent methylene hydrogens. These assignments were eventually borne out by subsequent chemical transformations. Confident of our stereochemical assignments, we sought to reduce the diols **11a/11b** to the olefin **2**.

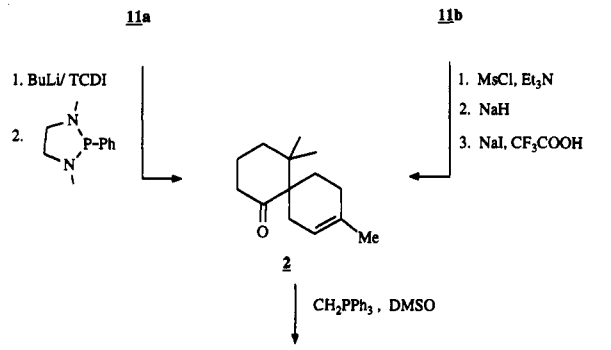
In general, the literature contains numerous methods to reduce *cis*-cyclohexanediols to olefins; however, we are aware of only a single procedure for the direct conversion of *trans*-cyclohexanediols to olefins. The method of Sharma et al., using TMSCl/NaI in CH_3CN, was attempted.[11] Cis keto diol **11a** afforded only a rearranged product, diketone **14**. The formation of **14** is rationalized via the iodohydrin TMS ether **13a**, which eliminates HI by an E_2 mechanism to give the TMS enol ether, which hydrolyzes to the ketone upon workup. In contrast, when the reaction was performed at 0 °C, trans keto diol **11b** gave a single iodohydrin intermediate, and its structure is tentatively assigned as indicated. When the iodohydrin **13b** was heated to 50 °C under the same reaction conditions (TMSCl/NaI in CH_3CN), a low yield (16%) of the desired ketone **2** was obtained. It was reasoned that the requisite trans diaxial arrangement of the iodo OTMS intermediate allows for this elimination in which iodide attacks at the iodo substituent. This process is inefficient due to the requirement of two large axial substituents on the cyclohexane ring (Scheme IV).

Given the facile separation of the cis and trans keto diols **11a** and **11b**, we adopted stereodivergent sequences to synthesize olefin **2**. The cis diol **11a** was converted to its corresponding thionocarbonate by treating the diol with BuLi (2 equiv) in DMF followed by addition of (thiocarbonyl)diimidazole (TCDI). The standard desulfurization and cheletropic elimination (1,1′-$(EtO)_3P$, 130 °C) proceeded poorly, but the more reactive 1,3-dimethyl-2-

Scheme IV



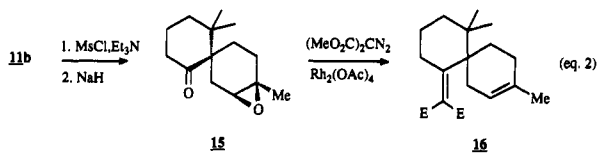
Scheme V



(±)-β-chamigrene **1**

phenyldiazaphospholidine is more efficacious, requiring lower temperatures.[11] Thus the olefin **2** was formed in 89% overall yield from keto diol **11a**. (Scheme V).

Though the trans diol **11b** could be converted to its corresponding thionocarbonate, the formation of the olefin through the cheletropic mechanism is not possible since this would require the formation of a trans double bond in a 6-membered ring. An alternate strategy involved the formation and deoxygenation of epoxide **15**. The epoxide **15** was formed according to the procedure outlined in eq 2. Reduction of the epoxide using the Ganem method[12]



(dimethyl diazomalonate/$Rh_2(OAc)_4$) formed the requisite olefin; however, further reaction at the carbonyl produced the malonate adduct **16** (eq 2). Attempts to reduce the formation of **16** by limiting the diazomalonate reagent resulted in lower yields of the desired olefin **3**. A more practical reduction of epoxide **15**, again relying on the work of Sharma,[13] was achieved by using NaI/CF_3CO_2H, giving olefin **2** in 67% yield. With both diols **11a,b** successfully transformed to olefin **2**, the completion of β-chamigrene was effected by using a Wittig procedure described by Ito,[2] thus completing the natural product synthesis (Scheme V).[14]

Conclusion

Methodology employing a $Rh_2(OAc)_4$-catalyzed intramolecular cyclopropanation to a dihydropyran derivative

(11) Chu, C. K.; Bhadi, V. S.; Doboszewski, B.; Gu, Z. P.; Kosugi, Y.; Pulliaiah, K. C.; Roey, P. V. *J. Org. Chem.* **1989**, *54*, 2217.

(12) Martin, M. G.; Ganem, B. *Tetrahedron Lett.* **1984**, *25*, 251.

(13) Sarma, D. N.; Sharma, R. P. *Chem. Ind. London* **1984**, *19*, 712.

(14) Spectral characteristics of our material are in accordance with the published data (see ref 3b).

was successfully realized. Furthermore, sequential bond fragmentations produced a [6.6] spirocyclic system with functionality suitably disposed for the eventual conversion to the natural product β-chamigrene. The synthesis proceeds in 14 steps from known intermediates and does not require the use of protecting groups. Though the synthesis provided the racemic natural product, optically active β-chamigrene could be produced in principle if dihydropyran 4 were resolved according to the method of Cervinka.[15] This has recently become an issue since β-chamigrene and derivatives have been identified as antiviral agents.[16]

Experimental Section

2-Hydroxy-6,6-dimethylcyclohexanemethanol (6). Under N_2, $LiAlH_4$ pellets (16.3 g, 0.43 mol) were added to diethyl ether (150 mL) and the mixture was stirred until the pellets dispersed (1 h). Keto ester 5[4] (20 g, 0.108 mol) in 400 mL of ether was added dropwise. The reaction was stirred for an additional hour and then quenched at 0 °C by adding H_2O (14 mL), 20% aqueous KOH (14 mL), and H_2O (40 mL), successively. The reaction mixture was stirred for an additional 15 min and then filtered. The solid paste was recovered, triturated with ether, and filtered again. The combined filtrates were dried ($MgSO_4$), filtered, and concentrated in vacuo to provide 12.8 g (77%) of 6, which was carried on with no further purification to the next step.

3,3-Dimethyl-2-((((4-methylphenyl)sulfonyl)oxy)methyl)cyclohexanol (7). A solution of diol 6 (25.6 g, 0.16 mol) in pyridine (260 mL) was stirred and cooled to 0 °C under N_2. *p*-Toluenesulfonyl chloride (31.4 g, 0.16 mol) was added. After 5 days the mixture was diluted with ether and washed with 10% HCl (2×), followed by brine (2×). Drying (Na_2SO_4) and evaporation of the solvent provided a crude oil, which was purified by chromatography on silica with hexane/ethyl acetate (4:1) to afford 39 g (78%) of tosylate 7: ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 0.92 (s, 3 H), 1.00–1.80 (m, 6 H), 2.45 (s, 3 H), 4.00–4.40 (m, 4 H), 7.35 (d, 2 H, J = 8.8 Hz), 7.85 (d, 2 H, J = 8.8 Hz); IR (KBr) 3600–3300 br, 3100–2800, 1600, 1570, 1460, 1430 cm^{-1}; exact mass (CH_4 CI, MH^+) calcd 313.1473, found 313.1305.

3,3-Dimethyl-2-methylenecyclohexanone (8). A solution of tosylate 7 (10 g, 0.032 mol) in acetone (200 mL) was treated with excess Jones reagent.[17] The solution was stirred at rt for 30 min. The acetone was evaporated and the residue was diluted with H_2O and extracted with ether (3×). The combined ether extracts were dried ($MgSO_4$) and evaporated to afford a clear oil in quantitative yield. The product was taken immediately to the next step: ^1H NMR (200 MHz, $CDCl_3$) δ 0.70 (s, 3 H), 1.10 (s, 3 H), 1.50–2.40 (m, 6 H), 2.50 (s, 3 H), 4.00–4.10 (m, 1 H), 4.35–4.45 (m, 1 H), 7.50 (d, 2 H, J = 8.8 Hz), 7.85 (d, 2 H, J = 8.8 Hz); IR (film) 3000–2900, 1710, 1360, 1190 cm^{-1}. To a solution of the keto tosylate obtained above (0.032 mol assumed) in benzene (200 mL) was added DBU (4.6 mL, 0.031 mol). The mixture was stirred for 2 h and then washed with H_2O and dried (Na_2SO_4). Evaporation of the solvent provided unstable enone 8 in quantitative yield, which was used immediately in the next step: ^1H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 6 H), 1.65–1.75 (m, 2 H), 1.80–2.00 (m, 2 H), 2.30–2.40 (m, 2 H), 5.15 (d, 1 H, J = 2 Hz), 5.55 (d, 1 H, J = 2 Hz).

Methyl 2,5,5-Trimethyl-5,6,7,8-tetrahydrochroman-2-carboxylate (4). A solution of enone 8 in benzene (50 mL) and methyl methacrylate (50 mL, 0.48 mol) containing hydroquinone (40 mg) was heated in a sealed vessel at 190 °C for 12 h. The cooled solution was poured into ether (800 mL) and the polymer side products were filtered and discarded. The ether was evaporated and a brown oil (5.0 g) was obtained. Two successive chromatographic purifications were carried out. First passage of the crude oil on silica using hexane/ethyl acetate (9:1) as the eluent; the second silica column used pet. ether/ether (20:1) as the eluent. Two products were obtained. The major product was dihydropyran ester 4 (3.35 g, 44%): ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 3 H), 1.00 (s, 3 H), 1.45 (s, 3 H), 1.10–1.45 (m, 3 H), 1.60–1.80 (m, 3 H), 1.85–2.15 (m, 3 H), 2.20–2.35 (m, 1 H), 3.70 (s, 3 H); IR (film) 3000–2840, 1740, 1680, 1450, 1380, 1200, 1140, 1100 cm^{-1}; MS m/e 239 $(MH)^+$, 223 $(M - CH_3)^+$, 207 $(M - OCH_3)^+$, 179 $(M - CO_2CH_3)^+$. The spectral data for the minor product (1.5 g, 13%) are consistent with the Diels–Alder dimer product (see Scheme II).

Diazo Ketone 9. A solution of the ester 4 (3.0 g, 12.6 mmol) in methanol (50 mL) was added to 1.0 N aqueous NaOH (12.6 mL, 12.6 mmol) and heated to reflux for 2 h. The solvent was evaporated and the residue dried over P_2O_5 at 90 °C for 3 h, resulting in a brown powder, Na salt (2.81 g, 90%): ^1H NMR (200 MHz, CD_3OD) δ 0.93 (s, 3 H), 0.96 (s, 3 H), 1.35 (s, 3 H), 1.35–1.50 (m, 2 H), 1.50–1.70 (m, 3 H), 1.80–2.10 (m, 3 H), 2.05–2.25 (m, 2 H). A suspension of the sodium salt (1.2 g, 4.87 mol) in methylene chloride (20 mL) containing a drop of DMF was cooled to 0 °C and treated with oxalyl chloride (540 μL, 4.87 mmol). The mixture was stirred at 0 °C for 15 min and then warmed to rt and added dropwise to a 0 °C solution of excess (0.5 M) CH_2N_2 in Et_2O. The reaction mixture was allowed to warm to rt overnight and the solvents were evaporated. The residue was purified by flash chromatography (95:5 hexane/ethyl acetate) to afford 9 as a yellow oil (1.49 g, 62%), which was used immediately in the next step: ^1H NMR (200 MHz, $CDCl_3$) δ 0.93 (s, 3 H), 0.97 (s, 3 H), 1.34 (s, 3 H), 1.50 (m, 1 H), 1.50–1.80 (m, 4 H), 1.80–2.10 (m, 4 H), 2.20–2.30 (m, 1 H), 5.61 (br s, 1 H); IR (film) 3000–2820, 2100, 1640, 1350 cm^{-1}. To a suspension of rhodium acetate dimer (8.2 mg, 0.018 mmol) in dry CH_2Cl_2 was added a solution of diazo ketone 9 (745 mg, 3.0 mmol) in CH_2Cl_2 (50 mL) dropwise over a 6-h period, using a syringe drive. The mixture was stirred for an additional 60 min and then quenched with 5% aqueous $NaHCO_3$. Separation of the organic phase, drying (Na_2SO_4), and evaporation of the solvent afforded 1.32 g (100%) of the desired cyclopropane 3, which was used immediately in the next step: ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (s, 3 H), 1.07 (s, 3 H), 1.19 (s, 3 H), 1.30–2.20 (m, 11 H); ^{13}C NMR (200 MHz, $CDCl_3$) 16.40, 17.51, 17.89, 25.22, 25.65, 26.39, 32.76, 34.45, 35.26, 36.82, 48.89, 75.83, 78.84, 211.82; IR (film) 3000–2800, 1720, 1150, 1120, 910 cm^{-1}; MS m/e 221 $(MH)^+$, 203 $(MH - H_2O)^+$. A solution of cyclopropane 3 (1.32 g, 6 mmol) in dry MeOH was stirred at 0 °C under N_2. A catalytic amount of camphorsulfonic acid was added. After 15 min 5% aqueous $NaHCO_3$ was added and the mixture was concentrated in vacuo and then diluted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated to produce an oil (1.37 g, 91%), methanol adducts 10a,b: ^1H NMR (200 MHz, $CDCl_3$) as a ~1:1 mixture of isomers δ 0.81 and 0.85 (2s, 6 H, ratio 1:1), 1.09 and 1.11 (2s, 6 H, ratio ~1:1), 1.15 and 1.16 (2s, 6 H), 1.20–2.20 (m, 24 H), 3.14 and 3.28 (2s, 6 H, ratio 1:1), IR (film) 3000–2800 br, 1740, 1190, 1090; MS m/e 253 $(MH)^+$, 235 $(MH - H_2O)^+$, 221 $(MH - CH_3OH)^+$; exact mass calcd 252.1725, found 252.1735.

5,5,9-Trimethyl-8β,9β-dihydroxyspiro[5.5]undecan-1-one (11a) and 5,5,9-Trimethyl-8α,9β-dihydroxyspiro[5.5]undecan-1-one (11b). A solution of methanol adducts 10a,b (1.27 g, 5.03 mmol) in dry MeOH (45 mL) was cooled to 0 °C and treated with $NaBH_4$ (210 mg, 5.5 mmol). The reaction was stirred at 0 °C for 30 min and then at rt for 60 min. A solution of 1 N aqueous NaOH was added, and the mixture was concentrated in vacuo and then diluted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and the solvent evaporated to give an oil (1.21 g, 95%) as a mixture of four isomers (spectral data not shown). To a solution of the above oil (1.21 g, 4.76 mmol) in 2:1 THF/H_2O at 0 °C was added several drops of 5% HCl. The mixture was stirred for 1 h and then concentrated in vacuo and diluted with CH_2Cl_2. The organic phase was washed with 5% aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated to afford 932 mg (82%) of a (1.3:1) mixture of cis and trans diols 11a and 11b, respectively. The two isomers were separated on a silica column, using hexane/ethyl acetate (1:1) as the eluent. Cis keto diol 11a: ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (s, 3 H), 0.91 (s, 3 H), 1.15 (s, 3 H), 1.40–2.60 (m, 12 H), 3.50–3.60 (m, 1 H), 4.60 (d, J = 6.0 Hz, 1 H); IR (film) 3500–3200, 3000–2820, 1695, 1140 cm^{-1}; MS m/e 241 $(MH)^+$, 223 $(MH - H_2O)^+$, 205 $(MH - 2H_2O)^+$; exact mass calcd 240.1725, found 240.1713. Trans keto diol 11b: ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (s, 6 H), 1.15 (s, 3 H), 1.40–2.70 (m, 12 H), 3.60–3.70 (m,

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1 H); IR (film) 3600–3100, 3000–2800, 1700 cm^{-1}; MS *m/e* 241 $(MH)^+$, 223 $(MH - H_2O)^+$, 205 $(MH - 2H_2O)^+$; exact mass calcd 240.1725, found 240.1734.

Cyclic Carbonates 12a and 12b. Samples of the separated diols **11a** and **11b** were converted to their corresponding cyclic carbonates. To solutions of the diols (5.0 mg, 0.019 mmol) respectively in DMF at rt were added 1,1'-carbonyldiimidazole (6.1 mg, 0.037 mmol) and catalytic (dimethylamino)pyridine. The mixtures were stirred for 60 min, then the DMF was removed in vacuo, and the residues were chromatographed on silica gel (hexane/ethyl acetate 7:3). Cis carbonate **12a**: ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.94 (s, 3 H), 1.47 (s, 3 H), 1.20–2.70 (m, 12 H), 4.39–4.43 (dd, J = 3.5, 5.3 Hz, 1 H); IR (film) 3000–2880, 1800, 1690, 1090 cm^{-1}; exact mass calcd 266.1518, found 266.1529. Trans carbonate **12b**: ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 0.98 (s, 3 H), 1.33 (s, 3 H), 1.50–2.70 (m, 12 H), 3.80–4.06 (dd, J = 13.5, 3.5 Hz, 1 H); IR (film) 3000–2880, 1800, 1690, 1090 cm^{-1}; exact mass calcd 266.1518, found 266.1539.

5,5,9-Trimethylspiro[5.5]undec-8-en-1-one (2). Method A. From Cis Keto Diol 11a. To a solution of the cis diol **11a** (150 mg, 0.625 mmol) in THF at 0 °C under N_2 was added nBuLi (695 μL 1.13 mmol) dropwise followed by 1,1'-(thiocarbonyl)diimidazole (192 mg, 1.075 mmol). The mixture was heated to reflux for 1 h and then cooled to 0 °C, and 1,3-dimethyl-2-phenyl-1,3-diaza-2-phospholidine was added dropwise. The mixture was stirred for 10 min at 0 °C and then heated to reflux for 2 days. The solvent was removed by distillation and the residue was chromatographed on silica gel (hexane/ethyl acetate 9:1) to afford 115 mg (89%) of keto olefin **2**. Spectral data for **2** are reported below in method C.

Method B. From Trans Keto Diol 11b, NaI, and TMSCl. To a stirred solution of the trans keto diol **11b** (24.2 mg, 0.10 mmol) in dry CH_3CN (1 mL) under N_2 was added NaI (91 mg, 0.6 mmol) in dry CH_3CN (1 mL), followed by freshly distilled TMSCl (101 μL, 0.8 mmol). The mixture was stirred overnight at rt, then diluted with CH_2Cl_2, washed with H_2O (2×) and aqueous $Na_2S_2O_3$ (2×), then dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography (hexane/ethyl acetate 9:1) to afford iodohydrin (Scheme IV, **13b**) in quantitative yield: ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.97 (s, 3 H), 1.24 (s, 3 H), 1.30–2.60 (m, 12 H), 4.70–4.80 (dd, J = 5.0, 12 Hz, 1 H); ^{13}C NMR (200 MHz, $CDCl_3$) δ 22.79, 23.54, 24.08, 24.36, 32.46, 35.41, 37.54, 37.98, 41.36, 49.60, 60.31, 70.11, 216.30; MS *m/e* 351 $(MH)^+$, 333 $(MH - H_2O)^+$, 223 $(MH - HI)^+$, 205 $(MH - HI - H_2O)^+$. Alternatively trans diol **11b** could be converted to olefin **2** without the isolation of the intermediate iodohydrin as follows. To a solution of **11b** (24.2 mg, 0.10 mmol) in dry CH_3CN (1 mL) under N_2, was added NaI (91 mg, 0.6 mmol) in dry CH_3CN (1 mL), followed by freshly distilled TMSCl (101 μL, 0.8 mmol). The mixture was heated to reflux for 48 h, then diluted with H_2O, and extracted with CH_2Cl_2 (3×). The combined organic layers were washed with H_2O (2×) and aqueous $Na_2S_2O_3$ (2×), then dried ($MgSO_4$), and concentrated. Purification by flash chromatography (hexane/ethyl acetate 9:1) afforded olefin **2**, 3.4 mg (16%). Spectral data are provided below in method C.

Method C. From Keto Epoxide 15. To a stirred solution of epoxide **15** vide infra (1.6 mg, 0.0072 mmol) and NaI (19 mg, 0.129 mmol) in CH_3CN (0.5 mL) at 0 °C was added CF_3CO_2H (3.2 mg, 0.029 mmol). The mixture was stirred for 15 min at 0 °C and then at rt for 1 h. The mixture was quenched with H_2O and extracted with CH_2Cl_2 (4×). The combined organic layers were washed with dilute aqueous $Na_2S_2O_3$, dried (Na_2SO_4), and concentrated in vacuo. Purification by flash chromatography (hexane/ethyl acetate 7:1) afforded 1.0 mg (67%) of keto olefin **2**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (s, 3 H, *gem*-dimethyl), 0.96 (s, 3 H, *gem*-dimethyl), 1.32 (dm, J = −13.5, 4.6, 3.6, 1.7 Hz, 1 H = 4eq), 1.60 (s (br), 3 H, C-9 methyl), 1.68 (m, 2 H), 1.79 (qt, J = −13.3, 13.3, 13.0, 4.6, 4.6 Hz, 1 H = 3ax), 1.84–1.88 (m, 3 H), 2.01 (td, J = −13.5, 13.3, 4.6 Hz, 1 H = 4ax), 2.20–2.21 (m, 2 H), 2.31 (d (br), J = −16.7 Hz, 1 H = 7 eq), 2.63 (td, J = −12.8, 13.0, 6.7 Hz, 1 H = 2ax), 5.38 (s (br), 1 H, olefinic H); IR 2959–2851, 1737, 1709, 1461, 800; exact mass calcd 206.16706, found 206.1672. Spectral data are in accordance with literature values.[18]

5,5,9-Trimethyl-8,9-epoxyspiro[5.5]undecan-1-one (15). To a stirred solution of trans diol **11b** (9.5 mg, 0.0395 mmol) and triethylamine (15.8 mg, 0.158 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added MsCl (18.0 mg, 0.158 mmol). The mixture was stirred for 45 min, then diluted with ether, and washed with brine (1×) and H_2O (1×). The aqueous layers were back extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo to afford crude epoxide, which was purified by flash chromatography (hexane/ethyl acetate 4:1) to give 5.4 mg (61%) of **15**: ^1H NMR (500 MHz, $CDCl_3$) δ 0.82 (s, 3 H, C-5 methyl), 0.92 (s, 3 H, C-5 methyl), 1.20 (ddd, J = −13.3, 10.8, 7.2 Hz, 1 H = 11ax), 1.25 (s, 3 H, C-9 methyl), 1.30 (m, 1 H = 4eq), 1.76 (ddd, J = −15.3, 7.2, 2.8 Hz, 1 H = 10eq), 1.80–1.86 (m, 4 H), 2.00 (dd, J = −15.3, 1.4 Hz, 1 H = 7ax), 2.22–2.24 (m, 2 H = 2eq and 10ax), 2.70 (td, J = −11.9, 11.9, 5.8 Hz, 1 H = 2ax), 2.77 (dt, J = −15.3, 2.8, 2.8 Hz, 1 H = 7eq), 3.06 (dt, J = 2.8, 1.4, 1.4 Hz, 1 H = C-8 methine); IR 2965–2871, 1703, 1260, 928, 758 cm^{-1}; exact mass calcd 222.1619, found 222.1633.

5,5,9-Trimethyl-1-methylenespiro[5.5]undec-8-ene ((±)-β-Chamigrene) (1). To a dry flask were added NaH (94 mg, 2.46 mmol 60%, suspension in oil) and freshly distilled DMSO (2 mL). The mixture was heated to 75–80 °C for 45 min. The solution was then cooled to 0 °C, methyltriphenylphosphonium bromide (929 mg, 2.6 mmol) in DMSO (4 mL) was added, and the reaction was stirred for 10 min until a clear yellow solution was obtained. The ketone **2** (85 mg, 0.41 mmol) in DMSO (1 mL) was added and the mixture was heated to 70 °C for 30 h. The reaction mixture was poured onto ice and extracted with Et_2O (3×). The organic phase was separated and dried ($MgSO_4$) and the solvent was distilled off. The residue was chromatographed on silica with pentane and the solvent was distilled to produce a colorless oil (68 mg, 85% yield). Bulb-to-bulb distillation under vacuum (100 mmHg) afforded pure (±)-β-chamigrene (**1**) (24 mg, 30%). Spectral data are in agreement with published data.[17]

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Supplementary Material Available: ^1H NMR spectra for compounds **1–4**, **8**, **10a,b**, **11a**, **11b**, **12a**, and **12b** (19 pages). Ordering information is given on any current masthead page.

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