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Diastereoselective Total Synthesis of (+)-13-Stemarene by Fourth Generation Methods: A Formal Total Synthesis of (+)-18-Deoxystemarin§

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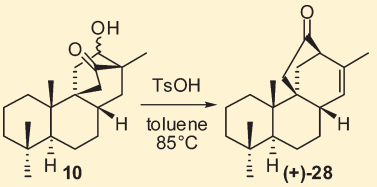
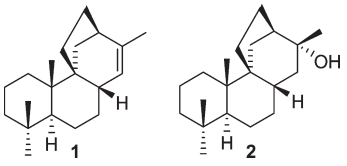
Supporting Information

ABSTRACT: The problem of constructing diastereoselectively the C/D ring system of stemarane diterpenes from a bicyclo[2.2.2]octane intermediate was solved resulting in very simple synthesis of (+)-13-stemarene **1**. The obtaining of the latter represents also a formal synthesis of (+)-18-deoxystemarin **2**. In the key step, the epimeric mixture **10**, dissolved in toluene, was converted by the action of TsOH into (+)-stemar-13-en-15-one **28**.



Stemarane diterpenes, characterized by the presence of a unique bicyclo[3.2.1]octane C/D ring system within the tetracyclic skeleton, were isolated in Central and South America from plants of the genus of *Stemodia*[1] and *Calceolaria*,[2−5] respectively. Stemarane diterpenes were also isolated in Japan from *Oryza sativa*, the plant of rice, which produces them in response to the invasion of the fungus *Pyricularia oryzae* or when exposed to UV radiation or heavy metals.[6,7] Finally, stemarane diterpenes were isolated from the fungus *Phoma betae*.[8] (+)-13-Stemarene **1**[8−10] and (+)-18-deoxystemarin **2**[9] are the simplest compounds in the stemarane family.



The first synthesis of a stemarane diterpene was reported in 1980 by Kelly and co-workers[11] who prepared stemarin (±)-**3**[1] from racemic podocarp-9(11)-en-12-one **4** by the Wiesner photochemical method[12] and by rearrangement[12−23] (Scheme 1) of tosylate **8** obtained from 6-*exo*-hydroxy-1-methyl-bicyclo[2.2.2]octan-2-one **6b** via bicyclo[2.2.2]octan-2-ol **7**. Given that **6b** was obtained as minor product of the intramolecular aldol condensation of 3-(2-oxoethyl)-cyclohexanone **5**,[24,25] the above-mentioned synthesis suffered from an inefficient nondiastereoselective step.

Thus, after having achieved by the same tools (i.e., the Wiesner photochemical method and the bicyclo[2.2.2]octane → bicyclo[3.2.1]octane rearrangement) the synthesis of aphidicolin and stemodane diterpenoids,[19−22,26] a diastereoselective route to the stemarane C/D ring system from a 6-hydroxy-1-methyl-bicyclo[2.2.2]octan-2-one intermediate represented a synthetic challenge to us.

Thus, we developed a procedure for the conversion of known **10a**,[27] the major product of the above-mentioned aldol reaction, into **12a** and applied it to the synthesis of (+)-**1** and (+)-**2** via **13** (Scheme 2).[9] We also described the preparation of key **10b** from the corresponding acetate **12b** by methanolysis in the presence of $CH_3ONa/La(OTf)_3$ (Scheme 2).[28]

More recently, we explored an approach based on the equilibration with TsOH in benzene at reflux of the ethylene dithioacetal epimeric mixture **14** (Scheme 3). A 6:4 equilibrium distribution in favor of the *exo* epimer **14b**, a precursor of key bicyclo[2.2.2]octan-2-ol **13**, was recorded. Epimers **14** were separated and the minor *endo* epimer **14a** was re-equilibrated. After three cycles, **14b** was obtained in a 92% diastereoisomeric excess. *Raney*-Ni reduction of the latter gave then **13**, already converted into (+)-**1** and (+)-**2**.[29]

Previously, an analogous approach starting from a 8(9)-podocarpen-14-one intermediate had been also explored, but the difficulties arisen in its conversion into the target compound forced us to abandon it.[30−32]

We wish now to present a new, general, and much simpler solution for the construction of stemarane diterpenes C/D ring system based on the existing *endo*/*exo* equilibrium under acidic conditions between 6-hydroxy-1-methyl-bicyclo[2.2.2]octan-2-ones (Scheme 1) and the acid catalyzed rearrangement of 6-*exo*-hydroxy-1-methyl-bicyclo[2.2.2]octan-2-ones to 4-methyl-bicyclo[3.2.1]oct-3-en-6-one.

The rearrangement of 6-hydroxy-1-methyl-bicyclo[2.2.2]-octan-2-one **15** to 4-methyl-bicyclo[3.2.1]oct-3-en-6-one[33] **16** had been described some years ago by Srikrishna and coworkers in the frame of a study on the reactivity of isotwistanes (Scheme 4),[34] but it was never applied to the synthesis of stemarane diterpenes.

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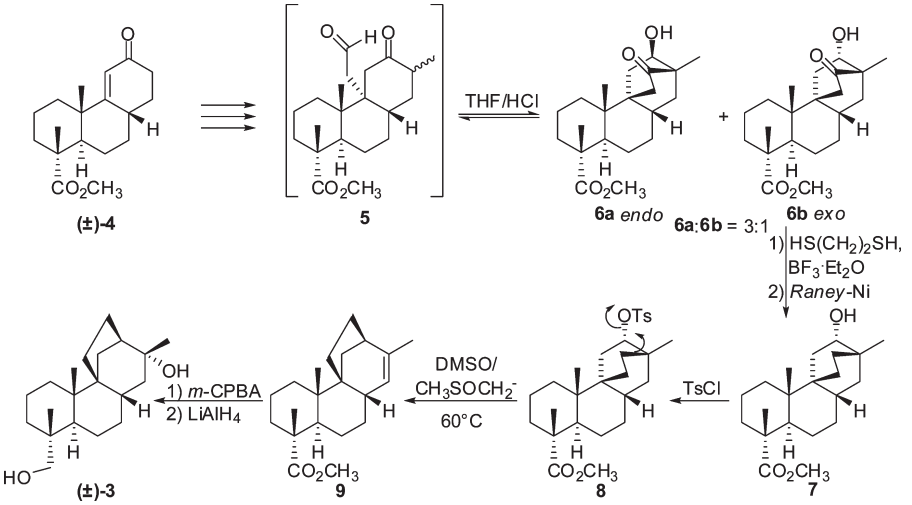
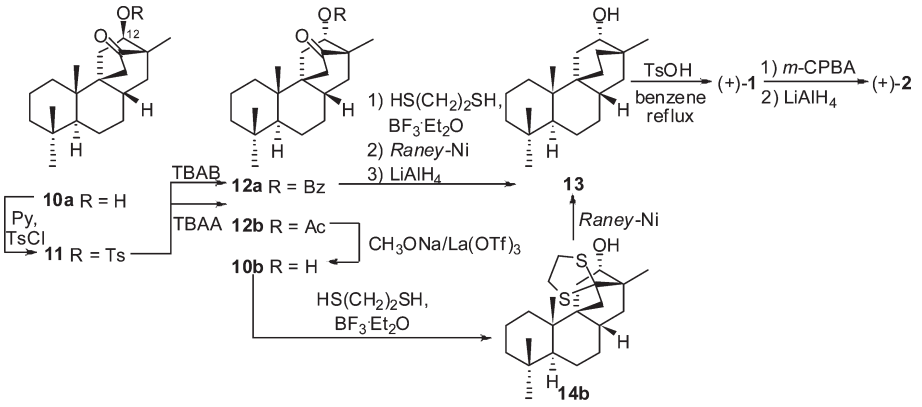
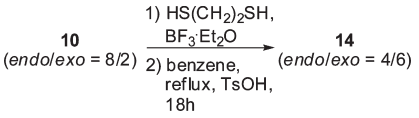
Scheme 1. R. B. Kelly's and Co-Workers' (±)-Stemarin (3) Total Synthesis



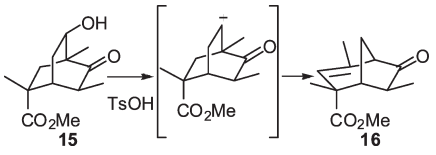
Scheme 2. Synthesis of (+)-13-Stemarene (1) and (+)-18-Deoxystemarin (2) by Inversion of the HO-C(12) Configuration



Scheme 3. Synthesis of (+)-13-Stemarene (1) and (+)-18-Deoxystemarin (2): Acid Catalyzed Equilibration of Ethylene Dithioacetals 14

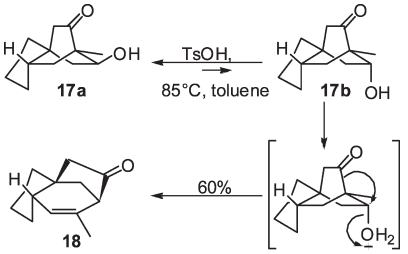


Scheme 4. The 6-Hydroxy-1-methyl-bicyclo[2.2.2]octan-2-one 15 → 4-Methyl-bicyclo[3.2.1]oct-3-en-6-one 16 Rearrangement As Proposed by Srikrishna et al.[34]



Since no experimental details were available in the literature,[34] before moving to the target compound, we adjusted the experimental conditions on known **17**,[28] available in seven steps from 2-methoxytetralin.

Scheme 5. Mechanistic Hypothesis for Conversion of 17 into 18



Best results were obtained when the epimeric mixture **17** dissolved in toluene was heated at 85 °C for 2 days in the presence of TsOH. The rearranged compound **18** was obtained cleanly as the only product (Scheme 5).

The role of the bridgehead methyl in stabilizing the carbocation resulting from the rearrangement was confirmed by the fact

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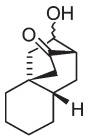
that when the same experimental conditions were applied to known **19**[35] no reaction occurred.



19

On the basis of the stereoelectronic requirements of the bicyclo[2.2.2]octane → bicyclo[3.2.1]octane rearrangement[12−23] and on the *endo*/*exo* 6-hydroxybicyclo[2.2.2]octan-2-one equilibrium, under the reaction conditions adopted, we propose for the rearrangement the rationale described in Scheme 5, where the protonated *exo* hydroxyl acts as the leaving group and the acyl group migration occurs from the *anti* side. The *endo* epimer does not undergo rearrangement because the carbonyl function at C(2) prevents the development of a positive charge on the adjacent bridged carbon.

After completing the model work, we then turned to the synthesis of (+)-13-stemarene **1** (Scheme 6). Our starting material was (−)-podocarp-9(11)-en-12-one **22**, the only product of a vinilogous equilibrium at C(8).[36] Compound (−)-**22** is available either from podocarpic acid **20**[37] or from (*S*)-5, 8a-dimethyl-3,4,8,8a-tetrahydronaphtalene-1,6(2H,7H)-dione **21**.[38]

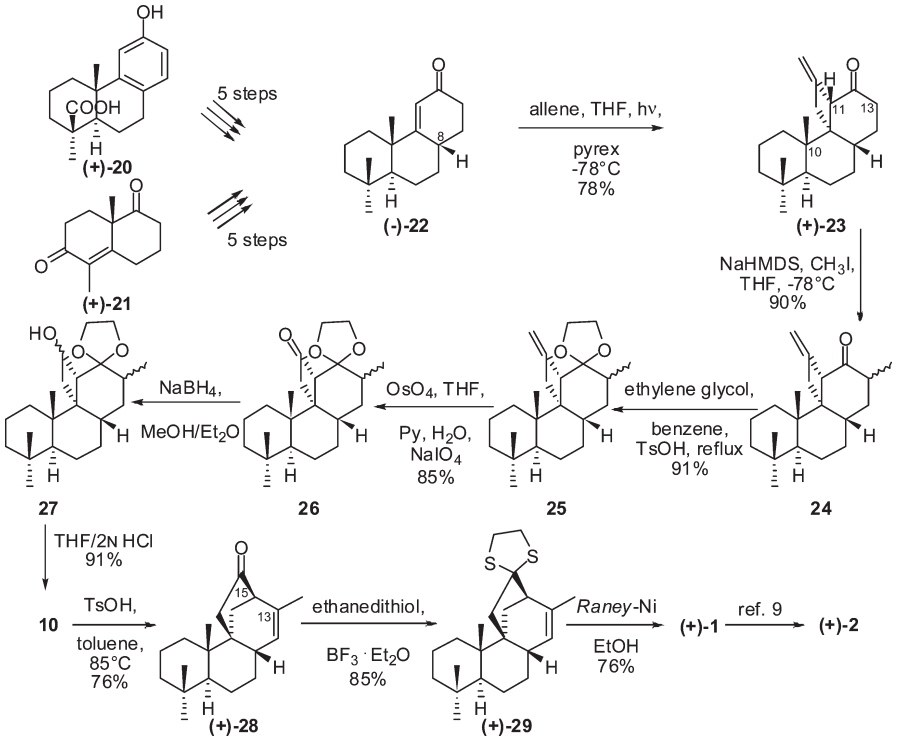
Photoaddition of allene to (−)-**22** in THF at −78 °C gave quantitatively the photoadduct **23**. The stereochemistry of the newly formed ring was established by NOESY experiments in which a cross-peak between the H−C(11) and CH_3−C(10) is present; the regiochemistry of the addition follows from the chemical shift of the H−C(11) which, being adjacent to both a double bond and a carbonyl function, is deshielded of about 1 ppm as compared to the H_2−C(13). Previously the regio- and stereochemistry of the addition had been established by the obtaining of the final compound.[19,27] Photoadduct (+)-**23** was then exposed to NaHMDS in THF at −78 °C. Upon addition of CH_3I in the presence of HMPA, the methylated photoadduct **24** was obtained. This methodology allowed us to shorten the previous procedure by two steps.[9,27] Compound **24** was converted into the acetal **25** and the exocyclic methylene cleaved with OsO_4/$NaIO_4$ to give the cyclobutanone **26**. Compounds **24**−**26** are mixtures of epimers at C(13). This stereochemical inhomogeneity is of no consequence since it will disappear when the bicyclo[2.2.2]octane system will be formed.

$NaBH_4$ reduction of **26** afforded then the cyclobutanol **27** which was used in the next step without purification. Thus treatment of **27** with a 2:1 THF/2 N HCl mixture caused deprotection of the carbonyl function unveiling an aldol system which underwent a retroaldol−aldol reaction giving **10** as an about 80:20 *endo*/*exo* epimeric mixture.[9,27] This equilibrium distribution is due to an unfavorable 1,3 boat-axial interaction experimented in the *exo* epimer by the *pseudo*-axially oriented hydroxy group.[25]

Since the intermediate characterizations of the synthesis of **10** from (−)-**22** were not fully described in the past,[9,19,27] we report also the experimental related to this section of the synthesis.

Thus, the mixture **10** was dissolved in toluene and heated at 85 °C in the presence of TsOH. Unlike the model compound, after 24 h, the rearrangement of **10** to (+)-**28** was complete. Thioacetalization of (+)-**28** with ethanedithiol and $BF_3 \cdot Et_2O$ at rt afforded then (+)-**29** which was transformed by the action of *Raney*-Ni in EtOH at 60 °C into (+)-**1**. Previous attempts to

Scheme 6. Regio- and Diastereoselective Synthesis of (+)-1 and (+)-2 from (−)-22 by the 6-Hydroxy-1-methyl-bicyclo-[2.2.2]octan-2-one → 4-Methylbicyclo[3.2.1]oct-3-en-6-one Rearrangement



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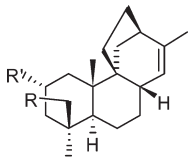
perform the deoxygenation of (+)-**28** via the corresponding hydrazone or tosylhydrazone were unsuccessful.

Compound (+)-**1** was identical to the compound previously prepared by us through the longer route.[9] Having (+)-**1** been previously converted into (+)-**2**, its obtainment represents also a formal diastereoselective total synthesis of the latter.

In conclusion, a simple and efficient synthesis of (+)-**1** from **10** was achieved. This approach is remarkable in that, owing to the stereospecificity of the rearrangement and to the 6-hydroxy-1-methyl-bicyclo[2.2.2]octan-2-ones *endo*/*exo* equilibrium, the whole 6-hydroxy-1-methyl-bicyclo[2.2.2]octan-2-ones *endo*/*exo* mixture is converted into the rearrangement product in which is also present the C(13)−C(14) double bond, a typical feature of some stemarane diterpenoids and a necessary tool for the introduction of the α configurated HO-C(13) when needed.

The approach to stemarane diterpenes via a 9(11)-podocarpen-12-one meets now all selectivity criteria. Besides, the correlation between the individual synthetic operations was brought to a maximum, ensuring high efficiency to the whole process.

Experiments are now in progress in our laboratory to extend this approach to the synthesis of more complex stemarin **3**,[1] 2-deoxyoryzalexin S **30**[2] and oryzalexin S **31**.[6,7]



30 R = OH, R' = H
31 R = OH, R' = OH

EXPERIMENTAL SECTION

General. All solvents were analytical grade. TLC: silica gel 60 F_{254}. Column Chromatography (CC): silica gel 60, 70−230 mesh ASTM. Mp uncorrected. IR Spectra: in cm^{-1}. ^1H and ^{13}C NMR (compounds **18**, **23**−**29**): at 300.13 and 75.48 MHz, respectively; δ in ppm relative to the residual solvent peak of C_6D_6 at 7.15 and 128.02 ppm and $CDCl_3$ at 7.26 and 77.0 ppm for ^1H and ^{13}C, respectively; ^1H and ^{13}C NMR (compound **1**): at 400.13 and 100.61 MHz, respectively; *J* in Hz. HPLC analysis: RID detector; analytical columns: EC 250/4 Nucleosil 100-5; EC 250/4 Nucleodur 100-5; EC 250/4 Nucleosil 100-5 C18; flow rate of 0.8 mL/min; semipreparative column: VP 250/10 Nucleodur 100-5; flow rate of 6 mL/min; t_R in min. TsOH was monohydrate.

Preparation of 18 from 17. A solution of **17** (68 mg; 0.33 mmol) and TsOH (62 mg, 0.33 mmol) in toluene (17 mL) was heated at 85 °C until TLC (Et_2O/*n*-hexane = 4/6, R_f **17** < R_f **18**) showed the disappearance of the starting material (≈ 48 h). After cooling to rt, the whole was diluted with Et_2O, washed with a saturated $NaHCO_3$ aqueous solution and finally with brine. After drying over anhydrous Na_2SO_4, the organic phase was filtered and evaporated to dryness under reduced pressure. The residue was purified by SiO_2 CC (Et_2O/*n*-hexane = 1/99) to give **18** (37 mg, 0.56 mmol) as an oil. Yield: 60%. IR ($CHCl_3$): 1732; ^1H NMR ($CDCl_3$): 5.26−5.41 (m, 1H), 2.62 (pd, *J* = 4.0, 1H), 1.92−2.22 (overlapped multiplets, 3H), 1.48−1.89 (overlapped multiplets, 9H), 1.04−1.45 (overlapped multiplets, 4H); ^{13}C NMR ($CDCl_3$): 210.5, 131.6, 128.3, 55.1, 51.6, 45.4, 39.4, 38.0, 32.1, 31.3, 26.4, 22.7, 22.0; MS: *m*/*z* = 190 (M^+, 21), 148 (45), 131(24), 119 (20), 105 (100%), 91 (68), 77 (30), 65 (19); HRMS: calcd. for $C_{13}H_{18}O$ [M + Na]$^+$: 213.1255; found 213.1261.

Preparation of (+)-23 from (−)-22. A Pyrex vessel containing a solution of (−)-9(11)podocarpen-12-one (−)-**22** (2.0 g, 8.1 mmol) in THF (25 mL) was cooled at −78 °C and an excess of allene was condensed. The solution was irradiated under Ar at −78 °C with a 500 W mercury vapor lamp until the TLC (Et_2O/*n*-hexane = 4/6, R_f **23** > R_f **22**) showed the disappearance of the starting material (≈4 h). The solution was allowed to warm-up slowly to rt and the solvent evaporated under reduced pressure. The residue was purified by SiO_2 CC (Et_2O/*n*-hexane = 1/9) to give (+)-**23** (1.8 g, 6.3 mmol) as a white solid. Yield: 78%. Mp (EtOH/H_2O = 96/4) 84.0−86.3 °C. $[\alpha]_D$ = +30.6 ($CHCl_3$, *c* = 2.3); IR (CCl_4): 1699; ^1H NMR ($CDCl_3$): 4.89 (sextet, *J* = 2.6, 2H), 3.51−3.40 (*m*, 1H), 2.80 (dt, J_t = 2.6, J_d = 17.5, 1H), 2.65−2.49 (overlapped multiplets, 2 H), 2.15 (dddd, J_d = 1.0, J_d = 7.5, J_d = 11.4, J_d = 19.0, 1H), 1.98−1.02 (overlapped multiplets, 13H), 0.97−0.86 (m, 1H), 0.84 (s, 3H), 0.83 (s, 3H), 0.79 (s, 3H). ^{13}C NMR ($CDCl_3$): 211.6, 141.1, 109.5, 55.5, 49.6, 46.4, 42.3, 39.1, 38.5, 36.5, 33.19, 33.16, 31.7, 31.4, 28.7, 25.3, 22.0, 21.2, 18.5, 15.9. GC-MS: 286 (M^+, 6), 271 (26), 253 (15), 243 (12), 229 (12), 215 (13), 211 (11), 201 (9), 189 (43), 173 (36), 161 (30), 145 (37), 133 (40), 119 (50), 105 (67), 91 (82), 83 (55), 69 (57), 55 (100). HPLC: column, Nucleosil; eluent, AcOEt/*n*-hexane 5/95, t_R = 8.0, purity 99%.

Preparation of 24 from (+)-23. A solution of sodium bis(trimethylsilyl)amide (NaHMDS, 5.5 mL, 1 M in THF, 5.5 mmol) was added at −78 °C to a solution of (+)-**23** (1.5 g, 5.2 mmol) in THF (185 mL). After 1 h at the same temperature, the resulting sodium enolate was added to a solution of CH_3I (0.65 mL, 10 mmol) in hexamethylphosphoramide (HMPA, 2.8 mL, 16 mmol). The solution was stirred at −78 °C until the TLC (Et_2O/*n*-hexane = 3/7) showed the disappearance of the starting material (≈ 3 h). The reaction mixture was allowed to warm to rt, and after neutralization with 2 N HCl, the solution was diluted with Et_2O, washed with brine, and dried over anhydrous Na_2SO_4. The organic phase was then filtered and evaporated to dryness under reduced pressure. The residue was purified by SiO_2 CC (Et_2O/*n*-hexane = 10/90) to give **24** as a C-(13) diastereoisomeric mixture of **24a** and **24b** (1.4 g, 4.7 mmol, **24a**/**24b** = 74:26; R_f **24a** > R_f **24b**). Yield: 90%. The mixture of the two diastereoisomers was purified by semipreparative HPLC (column, Nucleodur; eluent, AcOEt/*n*-hexane 1:99). (+)-**24a**: Mp (EtOH/H_2O = 96/4) 86.1−87.6 °C. $[\alpha]_D$ = +37.0 (*n*-hexane *c* = 2.4); IR (CCl_4): 1697; ^1H NMR (C_6D_6): 4.90 (dt, J_d = 2.6, J_t = 2.7, 1H), 4.80 (dt, J_d = 2.6, J_t = 2.5, 1H), 3.65−3.52 (m, 1 H), 2.67−2.47 (m, 2H), 2.42−2.26 (m, 1H), 1.99 (td, J_t= 8.4, J_d = 13.5, 1H), 1.61 (tt, *J* = 3.3, *J* = 12.7, 1H), 1.52−0.84 (overlapped multiplets, 14 H), 0.79 (s, 3H), 0.71 (s, 3H), 0.68 (s, 3H), 0.67−0.65 (m, 1H). ^{13}C NMR ($CDCl_3$): 212.5, 142.4, 109.2, 55.9, 51.1, 46.5, 42.4, 39.4, 39.2, 34.3, 33.2, 33.1, 32.6, 31.7, 30.9, 28.9, 22.0, 21.3, 18.7, 17.6, 15.5. GC-MS: 300 (M^+, 6), 285 (15), 267 (10), 257 (16), 243 (11), 229 (10), 215 (15), 201 (11), 189 (96), 176 (28), 161 (47), 147 (35), 133 (53), 119 (58), 105 (73), 91 (97), 81 (63), 69 (75), 55 (100). HPLC: analytical column, Nucleodur; eluent, AcOEt/*n*-hexane 1/99, t_R = 9.8, purity 100%. (−)-**24b**: Mp (EtOH/H_2O = 96/4) 82.4−83.4 °C. $[\alpha]_D$ = −10.5 (*n*-hexane, *c* = 3.0); IR (CCl_4): 1697; ^1H NMR (C_6D_6): 5.06 (q, *J* = 2.8, 1H), 4.81 (dt, J_d = 2.9, J_t = 2.4, 1H), 3.60−3.47 (m, 1 H), 2.50 (A of ABX_2, J_{AB} = 17.4, J_{AX} = 2.6, 1H), 2.30 (B of $ABMX_2$, J_{AB} = 17.4, J_{BX} = 2.7, J_{BM} = 3.1, 1H) 1.99−1.80 (m, 1H), 1.59−0.85 (overlapped multiplets, 16H), 0.81 (s, 3H), 0.77−0.70 (overlapped multiplets, 4H), 0.64 (s, 3H). ^{13}C NMR (C_6D_6): 210.1, 141.6, 109.2, 55.1, 49.4, 46.5, 45.5, 42.4, 39.0, 36.7, 34.1, 33.2, 33.1, 31.7, 31.6, 28.7, 22.2, 21.3, 19.2, 18.7, 15.9. GC-MS: 300 (M^+, 2), 285 (16), 267 (5), 257 (10), 244 (8), 229 (9), 215 (14), 201 (8), 189 (100), 173 (24), 161 (33), 145 (29), 133 (41), 119 (45), 105 (53), 91 (78), 81 (43), 69 (61), 55 (76). HPLC: analytical column, Nucleodur; eluent, AcOEt/*n*-hexane 1/99, t_R = 13.0, purity 100%.

Preparation of 25 from 24. A solution of **24** (1.4 g, 4.7 mmol), ethane-1,2-diol (15 mL, 0.27 mol), and TsOH (45 mg, 0.24 mmol) in benzene (0.20 L) was placed into a two-neck flask fitted with a

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Dean−Stark apparatus, a condenser, and a $CaCl_2$ tube. The mixture was then heated to reflux until the TLC (Et_2O/*n*-hexane = 1/9) showed the disappearance of the starting material (≈24 h). After cooling to rt, the mixture was poured into a separatory funnel, diluted with Et_2O and washed with a saturated $NaHCO_3$ solution, and dried over anhydrous Na_2SO_4. The organic phase was then filtered and evaporated to dryness under reduced pressure. The residue was purified by SiO_2 CC (Et_2O/*n*-hexane = 4/96) to give **25** (1.5 g, 4.3 mmol) as a C-(13) diastereoisomeric mixture of **25a** and **25b** (**25a**/**25b** = 32:68; R_f **25a** > R_f **25b**). Yield: 91%. The mixture of the two diastereoisomers was purified by semipreparative HPLC (column, Nucleodur; eluent, AcOEt/*n*-hexane 0.5:99.5). (−)-**25a**: Mp (EtOH/H_2O = 96/4) 140.4−141.5 °C. $[\alpha]_D$ = −47.6 (*n*-hexane, *c* = 2.1); ^{1}H NMR (C_6D_6): 5.54−5.44 (m, 1H), 5.04−4.95 (m, 1H), 3.59−3.41 (m, 4H), 2.97 (bs, 1H), 2.62−2.38 (m, 2H), 2.20−2.01 (m, 2H), 1.76−1.21 (overlapped multiplets, 13H), 1.12 (s, 3H), 1.10−0.89 (overlapped multiplets, 3H), 0.86 (s, 3H), 0.85 (s, 3H). ^{13}C NMR (C_6D_6): 144.6, 111.3, 109.5, 64.3, 63.5, 49.0, 47.2, 46.9, 42.6, 39.3, 39.0, 35.7, 33.5, 33.2, 32.4, 32.1, 31.0, 29.2, 22.3, 21.5, 20.4, 19.0, 15.7. GC−MS: 344 (M^+, 9), 329 (4), 205 (9), 113 (100), 105 (7), 100 (11), 91 (11), 73 (15), 69 (16), 55 (14). HPLC: analytical column, Nucleodur; eluent, AcOEt/*n*-hexane 1/99, t_R = 6.6, purity 100%. (+)-**25b**: Mp (EtOH/H_2O = 96/4) 138.6−140.1 °C. $[\alpha]_D$ = +54.3 (*n*-hexane, *c* = 2.3); ^{1}H NMR (C_6D_6): 5.37−5.29 (m, 1H), 5.03−4.95 (m, 1H), 3.65−3.44 (m, 4H), 2.87−2.76 (m, 1H), 2.55−2.32 (m, 3H), 2.24−2.05 (m, 1H), 1.71−1.06 (overlapped multiplets, 11H), 1.03 (d, *J* = 6.8, 3H), 0.99 (s, 3H), 0.96−0.87 (m, 1H), 0.86 (s, 3H), 0.83 (s, 3H), 0.83−0.70 (m, 1H). ^{13}C NMR (C_6D_6): 146.2, 113.5, 108.8, 65.3, 64.6, 49.5, 48.2, 47.0, 42.6, 39.2, 35.9, 33.5, 33.2, 31.8, 31.3, 30.8, 30.6, 30.2, 22.3, 21.6, 18.9, 15.9, 15.2. GC-MS: 344 (M^+, 12), 329 (6), 205 (10), 113 (100), 105 (6), 100 (12), 91 (11), 79 (6), 73 (15), 69 (17), 55 (13). HPLC: analytical column, Nucleodur; eluent, AcOEt/*n*-hexane 1/99, t_R = 8.1, purity 100%.

Preparation of 26 from 25. A solution of OsO_4 (30 mg, 0.12 mmol), pyridine (0.6 mL), and H_2O (12 mL) was treated with a solution of **25** (1.4 g, 4.1 mmol) in THF (60 mL). After stirring in the dark for 10 min, the solution was treated with a suspension of $NaIO_4$ (7.2 g, 33 mmol) in H_2O (24 mL) and the resulting mixture was stirred in the dark until the TLC (Et_2O/*n*-hexane = 3/7) showed the disappearance of the starting material (≈120 h). The suspension was filtered through a Celite pad, and the filtrate was diluted with Et_2O, while the organic phase was washed with H_2O, brine and dried over anhydrous Na_2SO_4. The organic phase was then filtered and evaporated to dryness under reduced pressure. The residue was purified by SiO_2 CC (Et_2O/*n*-hexane = 3/7) to give **26** (1.2 g, 3.5 mmol) as a C-(13) diastereoisomeric mixture of **26a** and **26b** (**26a**/**26b** = 23:77; R_f **26a** > R_f **26b**). Yield: 85%. (+)-**26a**: Mp (*n*-hexane) 166.4−167.8 °C. $[\alpha]_D$ = +23.0 (CCl_4, *c* = 2.1); IR (CCl_4): 1780; ^{1}H NMR (C_6D_6): 4.10−3.91 (m, 1H), 3.76 (td, J_d = 4.0, J_t = 6.7, 1H), 3.60 (ddd, *J* = 4.0, *J* = 6.7, *J* = 7.7, 1H), 3.48−3.27 (m, 1H), 3.11−2.95 (m, 2H), 2.53 (dd, *J* = 7.3, *J* = 16.9, 1H), 1.74−1.53 (m, 2H), 1.52−0.83 (overlapped multiplets, 15H), 0.78 (s, 3H), 0.76 (s, 3H), 0.73 (s, 3H), 0.72−0.62 (m, 1H). ^{13}C NMR (C_6D_6): 203.0, 110.1, 67.1, 65.9, 65.0, 47.2, 47.0, 46.4, 42.3, 40.6, 40.2, 36.4, 34.3, 33.4, 33.2, 32.4, 30.1, 22.7, 21.1, 18.8, 16.5, 14.5. GC-MS: 346 (M^+, 1), 134 (55), 120 (10), 113 (45), 100 (8), 91 (11), 87 (100), 79 (9), 69 (17), 55 (18). HPLC: analytical column, Nucleodur; eluent, AcOEt/*n*-hexane 10/90, t_R = 4.8, purity 100%. (+)-**26b**: Mp (*n*-hexane) 152.1−153.8 °C. $[\alpha]_D$ = +52.1 (CCl_4, *c* = 2.2); IR (CCl_4): 1776; ^{1}H NMR (C_6D_6): 3.67−3.35 (m, 4H), 3.02 (dd, *J* = 1.8, *J* = 4.2, 1H), 2.67 (A of ABX, J_{AB} = 18.4, J_{AX} = 4.2, 1H), 2.59 (B of ABX, J_{AB} = 18.4, J_{BX} = 1.8, 1H), 2.28−2.10 (m, 1H), 1.76−1.59 (m, 1H), 1.59−0.97 (overlapped multiplets, 11H), 0.94 (d, *J* = 6.7, 3H), 0.90 (s, 3H), 0.86−0.53 (overlapped multiplets, 8H). ^{13}C NMR (C_6D_6): 205.0, 111.1, 65.02, 65.00, 64.0, 47.7, 46.9, 46.2, 42.2, 39.2, 35.1, 33.8, 33.3, 33.1, 31.5, 31.0, 30.0, 22.2, 21.4, 18.6, 15.7, 15.5. GC−MS: 346 (M^+, 1), 262 (6), 134 (81), 126 (5), 120 (17), 113 (100), 105 (14), 100 (16), 91 (16), 86 (66), 79 (11), 69 (25), 55 (22). HPLC: analytical column, Nucleodur; eluent, AcOEt/*n*-hexane 10/90, t_R = 9.4, purity 100%.

Preparation of 10 from 26. A solution of **26** (1.13 g, 3.3 mmol) in Et_2O/MeOH 1:1 (65 mL) was treated with $NaBH_4$ (0.65 g, 17 mmol) at 0 °C. The resulting mixture was stirred until the TLC (Et_2O/*n*-hexane = 3/7) showed the disappearance of the starting material (≈15 min). H_2O was then added slowly at 0 °C to quench the excess of $NaBH_4$. After neutralization with 2 N HCl, the solution was diluted with Et_2O, washed with brine, and dried over anhydrous Na_2SO_4. The organic phase was then filtered and evaporated to dryness under reduced pressure to give **27** (1.1 g) which was used as such in the next step.

A solution of the crude **27** (1.1 g) in THF/2 N HCl 4:1 (140 mL) was refluxed until the TLC (Et_2O/*n*-hexane = 6/4) showed the disappearance of the starting material (≈ 12 h). After cooling to rt, the whole was diluted with Et_2O, washed with a saturated $NaHCO_3$ aqueous solution and finally with brine. After drying over anhydrous Na_2SO_4, the organic phase was filtered and evaporated to dryness under reduced pressure. The residue was purified by SiO_2 CC (AcOEt/*n*-hexane = 35/65) to give **10** (0.93 g, 3.0 mmol) as a C-(13) diastereoisomeric mixture of **10a** and **10b** (**10a**/**10b** = 80:20; R_f **10a** < R_f **10b**). Yield: 91%. (+)-**10a**: Mp (*n*-hexane) 145.9−147.0 °C. $[\alpha]_D$ = +22.3 ($CHCl_3$, *c* = 2.0); IR ($CHCl_3$): 1713; ^{1}H NMR (C_6D_6): 3.54 (dt, J_t = 3.6, J_d = 9.2, 1H), 2.58 (d, *J* = 4.1, 1H), 2.29 (ddd, *J* = 3.5, *J* = 9.2, *J* = 14.3, 1H), 2.19 (A of AB, J_{AB} = 18.4, 1H), 1.99 (B of ABX, J_{AB} = 18.4, J_{BX} = 3.5, 1H), 1.55−0.90 (overlapped multiplets, 17H), 0.86 (s, 3H), 0.79 (s, 3H), 0.70 (s, 3H), 0.62 (q, *J* = 10.8, 1H). ^{13}C NMR (C_6D_6): 214.3, 74.0, 48.9, 46.3, 44.3, 43.3, 42.3, 38.6, 38.2, 34.4, 33.7, 33.33, 33.29, 33.0, 32.7, 22.5, 22.4, 19.0, 16.7, 16.1. GC−MS: 304 (M^+, 6), 260 (24), 244 (41), 176 (11), 165 (12), 159 (8), 150 (13), 145 (7), 135 (24), 120 (100), 105 (53), 91 (38), 81 (41), 69 (59), 55 (59). HPLC: analytical column, Nucleodur; eluent, AcOEt/*n*-hexane 30/70, t_R = 7.0, purity 99%. (+)-**10b**: Mp (*n*-hexane/Et_2O) 211.6−212.7 °C. $[\alpha]_D$ = +50.7 ($CHCl_3$, *c* = 2.2); IR ($CHCl_3$): 1709; ^{1}H NMR (C_6D_6): 3.32−3.17 (m, 1H), 1.93−1.69 (overlapped multiplets, 3H), 1.67−0.86 (overlapped multiplets, 19H), 0.83 (s, 3H), 0.79 (s, 3H), 0.68 (s, 3H). ^{13}C NMR (C_6D_6): 214.4, 70.2, 49.0, 46.2, 44.2, 42.4, 42.1, 38.7, 34.3, 33.3, 33.25, 33.23, 33.0, 31.9, 31.5, 22.5, 22.4, 19.0, 16.4, 15.8. GC−MS: 304 (M^+, 12), 286 (11), 260 (59), 244 (38), 176 (21), 165 (25), 147 (30), 135 (32), 123 (73), 105 (60), 91 (57), 81 (68), 69 (100), 55 (87). HPLC: analytical column, Nucleodur; eluent: AcOEt/*n*-hexane 30/70, t_R = 5.2, purity 99%.

Preparation of (+)-28 from 10. A solution of **10** (0.23 g; 0.74 mmol) and TsOH (0.13 g, 0.69 mmol) in toluene (37 mL) was heated at 85 °C until TLC (Et_2O/*n*-hexane = 1/1, R_f **10** < R_f (+)-**28**) showed the disappearance of the starting material (≈24 h). After cooling to rt, the whole was diluted with Et_2O, washed with a saturated $NaHCO_3$ aqueous solution and finally with brine. After drying over anhydrous Na_2SO_4, the organic phase was filtered and evaporated to dryness under reduced pressure. The residue was purified by SiO_2 CC (Et_2O/*n*-hexane = 5/95) to give (+)-**28** (0.16 g, 0.56 mmol) as a white solid. Yield: 76%. Mp (*n*-hexane) 67.3−68.2 °C. $[\alpha]_D$ = 546.8 ($CHCl_3$, *c* = 1.96); UV (CH_3CN): λ_{max}291 nm (ε = 432 M^{-1} cm^{-1}), λ_{max} 218 nm (ε = 3451 M^{-1} cm^{-1}); IR (CCl_4): 1738; ^{1}H NMR (C_6D_6): 0.72 (s, 3H), 0.77 (s, 3H), 0.81 (s, 3H), 0.87−1.54 (overlapped multiplets, 12H), 1.56−1.63 (m, 1H), 1.65 (ps, 3H), 1.82 (B of ABX, J_{AB} = 18.4, J_{BX} = 1.7, 1H), 1.85−1.95 (m, 1H), 2.08 (A of AB, J_{AB} = 18.4, 1H), 2.52 (ps, 1H), 5.05−5.20 (m, 1H); ^{13}C NMR (C_6D_6): 17.0, 18.8, 21.7, 22.48, 22.52, 26.3, 32.0, 32.6, 33.4, 34.0, 38.8, 42.31, 42.33, 43.9, 47.6, 47.9, 55.4, 128.6, 131.5, 207.7; MS: *m*/*z* = 286 (M^+, 34), 271 (10), 244 (8), 229 (6), 215 (6), 159 (8), 147 (18), 131 (12), 118 (28), 106 (100%), 91 (40), 81 (21), 69 (30). HRMS: calcd. for $C_{20}H_{30}O$ $[M + Na]^+$: 309.2194; found 309.2206; HPLC: eluent, AcOEt/*n*-hexane 4/96; t_R: 8.0 min, purity 99%.

Preparation of (+)-29 from (+)-28. To a solution of (+)-**28** (60 mg, 0.21 mmol) in 1,2-ethanedithiol (0.40 mL, 4.8 mmol), cooled to 0 °C, $BF_3 \cdot Et_2O$ (0.2 mL, 1.3 mmol) was added while stirring. When TLC analysis (*n*-hexane/Et_2O = 9/1, R_f (+)-**28** < R_f (+)-**29**) showed the disappearance of the starting material (≈10 min), the mixture was poured into a separatory funnel, diluted with CH_2Cl_2 (10 mL) and washed with 2 N NaOH (3 × 2 mL). The organic phase was washed with H_2O until neutral and finally with brine. It was dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude mixture was purified by SiO_2 CC (*n*-hexane/AcOEt = 99/1) to give (+)-**29** (65 mg, 0.18 mmol) as a white solid. Yield: 85%. Mp (MeOH/Et_2O) 163.5−164.5 °C. $[\alpha]_D$ = 111.9 ($CHCl_3$, *c* = 1.46); ^{1}H NMR ($CDCl_3$): 0.81 (s, 3H), 0.84 (s, 3H), 0.91 (s, 3H), 0.96−1.77 (overlapped multiplets, 12H), 1.81 (ps, 3H), 1.94 (B of AB, J_{AB} = 14.8, 1H), 2.00 (dd, *J* = 3.9, *J* = 11.7, 1H), 2.06−2.20 (m, 1H), 2.32 (d, *J* = 3.5, 1H), 2.48 (A of AB, J_{AB} = 14.8, 1H), 3.13−3.43 (m, 4H), 5.07−5.18 (m, 1H); ^{13}C NMR ($CDCl_3$): 137.2, 127.0, 76.6, 56.2, 50.4, 50.3, 48.4, 44.6, 42.4, 40.0, 39.2, 38.7, 33.9, 33.4, 32.8, 31.1, 30.2, 24.6, 22.4, 22.2, 18.6, 16.7. MS: *m*/*z* = 362 (26), 334 (11), 286 (9), 244 (29), 229 (6), 209 (6), 182 (14), 177 (6), 157 (12), 144 (21), 131 (23), 118 (35), 105 (100%), 91 (46), 81 (24), 69 (39); HRMS: calcd. for $C_{22}H_{34}S_2$ $[M + Na]^+$: 385.2000; found 385.2018. HPLC: eluent, AcOEt/*n*-hexane 0.5/99.5; t_R: 6.3 min, purity 99%.

Preparation of (+)-1 from (+)-29. A solution of (+)-**29** (54 mg, 0.15 mmol) in $EtOH_{abs}$ (20 mL) was stirred at 60 °C with *Raney*-Ni until the TLC analysis (*n*-heptane, R_f (+)-**29** < R_f (+)-**1**) showed the disappearance of the starting material (≈30 min). The catalyst was removed by filtration through a Celite pad and the solvent evaporated to dryness under reduced pressure. The crude mixture was purified by SiO_2 CC (*n*-heptane) to give (+)-**1** (31 mg, 0.11 mmol) as an oil. Yield: 76%. $[\alpha]_D$ = +66.9 ($CHCl_3$, *c* = 2.27). ^{1}H NMR ($CDCl_3$): 4.96 (dd, *J* = 0.9, *J* = 4.3, 1H), 2.18 (t, *J* = 4.5, 1H), 1.95−1.77 (m, 1H), 1.76−1.28 (overlapped multiplets, 16H), 1.27−1.05 (overlapped multiplets, 4H), 0.95 (s, 3H), 0.85 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$): 138.8, 124.2, 51.0, 49.2, 44.5, 43.3, 42.6, 38.9, 33.9, 33.5, 33.4, 32.6, 31.9, 31.7, 29.9, 22.4, 22.3, 22.2, 18.8, 16.8. GC−MS: 272 (38), 257 (87), 229 (27), 213 (17), 201 (14), 187 (26), 175 (22), 161 (40), 147 (30), 131 (31), 125 (35), 119 (47), 105 (100), 91 (74), 81 (58), 77 (34), 69 (55), 65 (14), 55 (70). HPLC: analytical column, Nucleosil C18; eluent, $(CH_3)_2CO/H_2O$ 95/5; t_R: 6.1 min, purity 99%.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H-and ^{13}C NMR spectra of all synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ DEDICATION

§Dedicated to Professor Goffredo Rosini on the occasion of his 70th birthday.

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