and brine, dried ($MgSO_4$), filtered, and evaporated under reduced pressure to give 314 mg of a yellow solid. Recrystallization of the solid material from dichloromethane–hexanes (three times) provided 258 mg (93%) of analytically pure **1d** as yellow needles: mp 251–252 °C; UV (EtOH) λ_{max} 216 nm (ϵ 27 000), 237 (33 800), 268 (28 000), 320 (5900), 384 (7500); ^1H NMR ($CDCl_3$) δ 2.10 (s, 3 H, CCH_3), 2.04 (d, J = 7 Hz, $CHCH_3$), 2.98 (s, 3 H, $ArCH_3$), 4.05 (s, 3 H, OCH_3), 6.35 (s, 1 H, COCH), 7.20–7.50 (m, 1 H, CH_3CH), 7.44 (d, J = 8 Hz, 1 H, Ar H), 7.91 (s, 1 H, Ar H); mass spectrum, m/e 374 ($M^{+\cdot}$), 295, 266.

Anal. Calcd for $C_{23}H_{18}O_5$: C, 73.79; H, 4.85. Found: C, 73.50; H, 4.95.

Acknowledgment. The authors express their appreciation to Dr. M. Furukawa, Daiichi Seiyaku Co., and Dr. Karl Dahm, Texas A&M University, for supplying spectral data on kidamycin and the indomycins, respectively. This work was generously supported by the National Cancer Institutes of the Department of Health, Education, and Welfare (Grant No. CA 18141).

Registry No. 1d, 73713-33-4; **2a**, 118-93-4; **2b**, 73713-34-5; **3**, 73713-35-6; **5**, 73713-36-7; **6a**, 6520-83-8; **6b**, 73713-37-8; **7a**, 73713-38-9; **7b**, 73318-26-0; **7c**, 65131-09-1; **8a**, 70151-05-2; **8b**, 70151-06-3; **8c**, 70151-07-4; **8d**, 70151-08-5; **8e**, 73713-39-0; **9a**, 70151-09-6; **9b**, 73713-40-3; **10**, 73713-41-4; **11**, 73713-42-5; **12a**, 70151-11-0; **12b**, 70151-12-1; **13**, 73713-43-6; **14**, 73713-44-7; **15**, 73713-45-8; tigloyl chloride, 35660-94-7; *N*-bromosuccinimide, 128-08-5; benzenethiol, 108-98-5; methyl *trans*-2-butenoate, 623-43-8; 3-penten-2-one, 625-33-2; tiglaldehyde, 497-03-0; *tert*-amyl alcohol, 75-85-4.

East Indian Sandalwood Oil. 2.[1] Stereoselective Synthesis of (±)-Epi-β-santalene and (±)-Epi-β-santalol[‡2]

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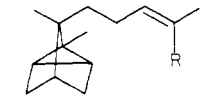
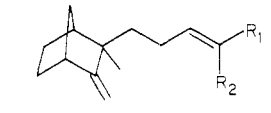
Acid-catalyzed rearrangement of γ-lactone **6** in the presence of acetonitrile provides a mixture of amide acids, which are readily separated as their ethyl esters **18–20**. The major product **18**, when subjected to fragmentation, provides esters **21** and **22** (92% and 8%, respectively). The structure of **21** has been confirmed by its conversion, via aldehyde **23**, to (±)-epi-β-santalene (**8**). Similarly, the structure of **22** has been confirmed by its conversion to (±)-α-santalene (**3**). (±)-Epi-*cis*-β-santalol (**9**), (±)-epi-*trans*-β-santalol (**10**), and (±)-dihydroepi-β-santalol (**11**) have also been prepared via aldehyde **23**.

Introduction

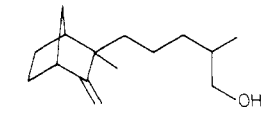
The oil which is obtained by steam distilling the heartwood of East Indian sandalwood trees is used in large quantities by the fragance industry for its sweet woody tenacious odor. α-Santalol (**1**) and β-santalol (**2**) account for up to 90% of the oil and are generally considered to be responsible for its main odor character. Many minor components of the oil have been identified, and undoubtedly some of them contribute to the overall odor character. α-Santalene (**3**), β-santalene (**4**), and dihydro-β-santalol (**5**) are all reported to have tenacious woody odors. Our previous synthesis of (±)-β-santalene and (±)-β-santalol from racemic camphene relied on the acid-catalyzed rearrangement of γ-lactone **6** to the δ-lactone **7**. Further investigation of this rearrangement in the presence of aliphatic nitriles has provided additional support for the mechanism proposed earlier and has resulted in the synthesis of (±)-epi-β-santalene (**8**) and the first syntheses of (±)-epi-*cis*-β-santalol (**9**), (±)-epi-*trans*-β-santalol (**10**), and (±)-dihydroepi-β-santalol (**11**).



1, R = CH_2OH
3, R = CH_3



2, R_1 = CH_3; R_2 = CH_2OH
4, R_1 = R_2 = CH_3



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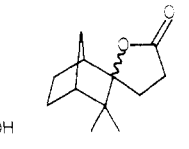

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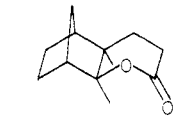

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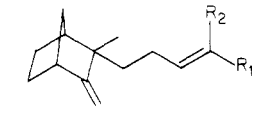
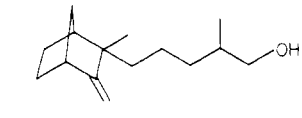


8, R_1 = R_2 = CH_3
9, R_1 = CH_3; R_2 = CH_2OH
10, R_1 = CH_2OH; R_2 = CH_3



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Discussion

We were interested in determining what effect the addition of aliphatic nitriles to the acid-catalyzed rearrangement of γ-lactone **6** would have on the equilibrium mixture of carbocations depicted in Scheme I and in particular whether the Ritter[3] adduct corresponding to cation **17** could be obtained preferentially. In the event, sulfuric acid catalyzed rearrangement of **6** in the presence of acetonitrile gave a mixture of amide acids. Esterification (ethanol, *p*-toluenesulfonic acid) gave a mixture of one major and two minor products, which were readily separated by preparative high-performance LC. Spectral data and mechanistic considerations suggested structures **18–20** for the three unknowns. The major product, when heated with *p*-toluenesulfonyl chloride in pyridine, gave a mixture

[‡] Dedicated to the memory of Dr. Ernest Guenther.

(1) Christenson, P. A.; Willis, B. J. *J. Org. Chem.*, **1979**, *44*, 2012.
(2) Part of this work was adumbrated at the 178th American Chemical Society Meeting, Division of Agricultural and Food Chemistry, Washington D.C., Sept 9, 1979, Paper No. 46.
(3) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.

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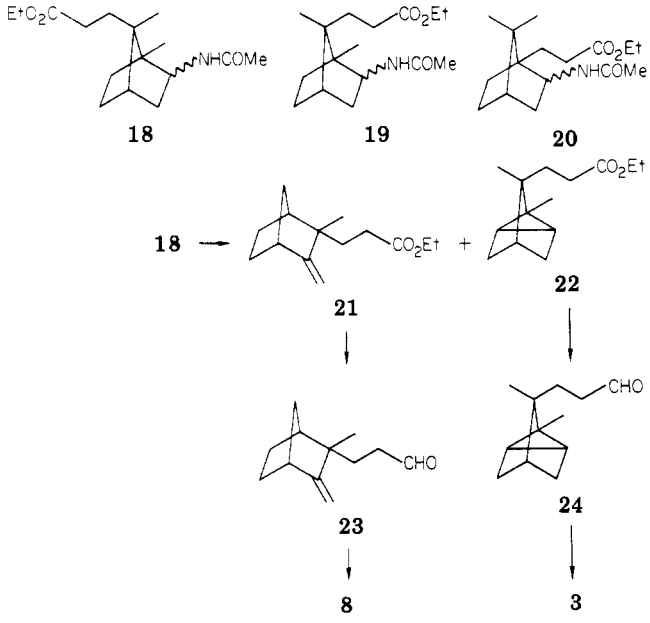
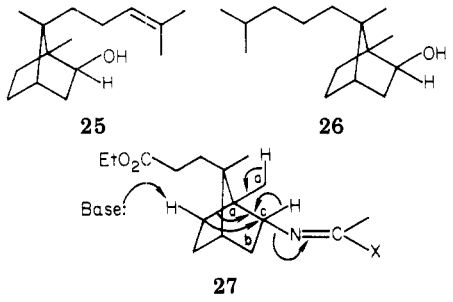


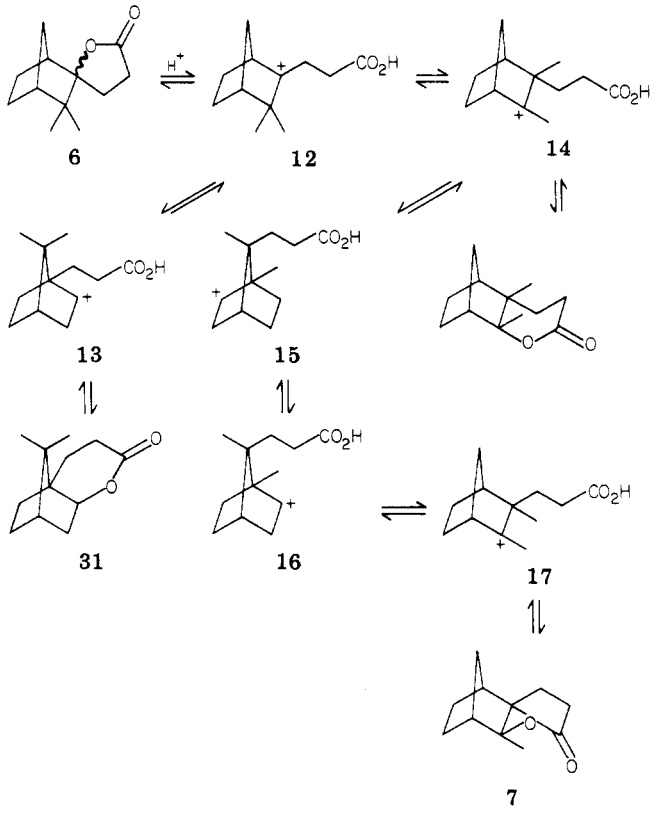
of esters **21** and **22** (92% and 8%, respectively) in 93% yield. The structure of ester **21** was confirmed by its conversion to (±)-epi-β-santalene (**8**) as follows. Reduction of **21** with diisobutylaluminum hydride gave aldehyde **23** in 91% yield. Reaction of **23** with isopropylidenetriphenylphosphorane gave **8** in 76% yield. Comparison of spectral data and GLC retention time for the synthetic material with those for natural epi-β-santalene (**8**) and β-santalene (**4**) (isolated from East Indian sandalwood oil) showed that the synthetic material contained 96% **8** and less than 1% **4**. Similarly ester **22** was converted via aldehyde **24** to (±)-α-santalene (**3**), which was identical with natural α-santalene.

Money has shown[4] that dehydration of isocampherenol (**25**) and isoepicampherenol (**26**) to β-santalene and epi-

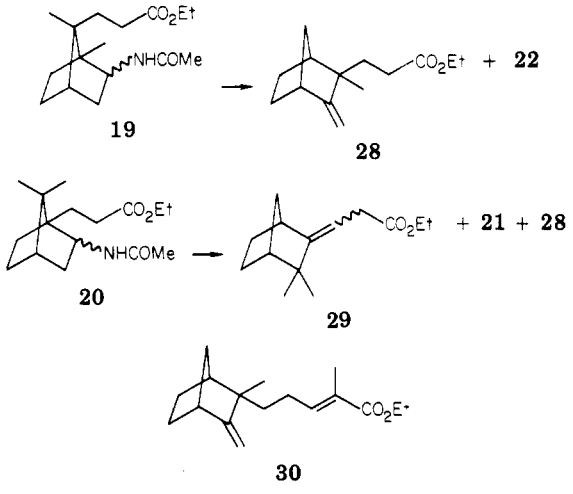


β-santalene is stereospecific. If an analogy with our fragmentation (formally a retro-Ritter reaction) is valid, amide ester **18**[5] would lead to ester **21**. Mechanistically, the formation of esters **21** and **22** may be rationalized in terms of an intermediate **27**. Elimination via path a would give rise to **21** whereas path b would give rise to **22**. Alternatively a carbene mechanism (path c) could also lead to **22**.[6] Examples of the retro-Ritter reaction have been

Scheme I



reported previously.[7] The reaction can also be considered a variation of the well-known and synthetically valuable Beckmann fragmentation. The two minor amide esters from the Ritter reaction were separately subjected to the fragmentation conditions. One gave a mixture of esters **28**[1] and **22** (88% and 9%, respectively) in 86% yield, which



by analogy are probably formed from the amide ester **19**. The other minor amide ester **20** gave a mixture containing 79% of ester **29**[1] and 3% each of esters **21** and **28** in 84% yield. Subjecting the crude mixture of amide esters to the fragmentation conditions provided a mixture of esters **21**, **28**, **22**, and **29** (61, 21, 7, and 11%, respectively) in 82% yield. Varying the Ritter reaction conditions led to higher yields of the adducts, but the ratio of esters obtained after fragmentation remained fairly constant. Representative experiments are shown in Table I. The isolation of the

(4) (a) Hodgson, G. L.; MacSweeney, D. F.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2113. (b) Eck, C. R.; Hodgson, G. L.; MacSweeney, D. F.; Mills, R. W.; Money, T. *J. Chem. Soc., Perkins Trans. 1* **1974**, 1938.

(5) In the ^{1}H NMR spectrum of **18** the singlet at δ 0.89 is assigned to the 1,7-dimethyl groups. In **19** the singlets at δ 0.83 and 0.87 are assigned to the 1,7-dimethyl groups, and in **20** the singlets at δ 0.87 and 0.97 are assigned to the 7,7-dimethyl groups. If the amide group in **18–20** has an effect on the chemical shift of the 7-methyl group similar to that of the hydroxyl group in the campherenols and borneols,[1,4] then the NMR data for **18–20** would suggest that the amide group has the endo configuration in **18** and **19** and the exo configuration in **20**. These tentative assignments are supported by the spectral data for 1,7,7-trimethyl-2-*exo*-(acetylamino)bicyclo[2.2.1]heptane reported by Kitagawa, N.; Nojima, M.; Tokura, N. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2369.

(6) Shapiro, R. H. *Org. React.* **1976**, *23*, 405.

(7) (a) Syhora, K.; Bočková, H. *Tetrahedron Lett.* **1965**, 2369. (b) Fêtizon, M.; Moreau, N. *Bull. Soc. Chim. Fr.* **1966**, 2404.

Table I

Ritter reaction[a]				esterification,	retro-Ritter reaction				
						ratio of esters			
mol % CH_3CN	time, h	temp, °C	yield, %	% yield	yield, %	21	28	22	29
200[b]	1.75	−5 to −10	65	94	82	61	21	7	11
200[c]	1.25	−5 to −12	81	92	94	63	18	7	12
2000[c]	0.75	−6 to −10	89	90	82	55	25	6	13
200[d] *i*-PrCN	3.0	−5 to −12	72	94	83	61	23	10	7

[a] 20 mL of concentrated sulfuric acid per gram of lactone **6** was used. [b] CH_3CN added over 1.5 h; stirred additional 0.25 h. [c] **6** added over 0.5 h. [d] *i*-PrCN added over 5 min.

Ritter adducts **18**, **19**, and **20**, corresponding to classical monocations **15**, **16**, and **13**, provides additional support for the mechanism proposed for the rearrangement of γ-lactone **6** to the δ-lactone **7**. Adduct **18** is favored on steric grounds and because, if dications are involved, it represents the intermediate where charge separation would be greatest.

The availability of aldehyde **23** permitted preparation of other members of the epi series of sandalwood compounds. Sequential treatment of **23** with ethylidenetriphenylphosphorane, *n*-butyllithium, and formaldehyde[8] gave (±)-epi-*cis*-β-santalol (**9**) in 34% yield. Reaction of aldehyde **23** with sodio(triethylphosphono)propanoate gave ester **30** as a mixture of trans/cis (9:1) isomers in 67% yield. Aluminum hydride reduction of **30** gave (±)-epi-*trans*-β-santalol (**10**) (containing 14% of the cis isomer) in 87% yield. Lithium/ammonia reduction of **30** gave (±)-dihydroepi-β-santalol (**11**) (77% theoretical), a known component of East Indian sandalwood oil.[9]

Experimental Section

General. Tetrahydrofuran was distilled from sodium and benzophenone. Acetonitrile, pyridine, dimethoxyethane, hexane, and toluene were dried over 4-Å molecular sieves. Moisture- or oxygen-sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere.

Spinning-band distillations were carried out with a Perkin-Elmer NFA-200 auto-annular still. GLC analyses were obtained with a Hewlett-Packard Model 5840A or a Perkin-Elmer Model 3920 gas chromatograph, using either a 10-ft 2-mm i.d. glass column packed with 2% Carbowax 20M on Chromosorb G 100/120 or a 12-ft 2-mm i.d. glass column packed with 3% OV-101 on Chromosorb WHP 100/120. Where indicated, precentages refer to computer-calculated peak areas without correction for response. ^1H NMR spectra were recorded with a Varian Associates T-60A or Bruker WP-80 spectrometer, using tetramethylsilane as internal reference. IR spectra were obtained with a Perkin-Elmer 137 Infracord. UV spectra were obtained with a Beckman Model DB-G grating spectrophotometer. Mass spectra were obtained with a Hewlett-Packard 5985 mass spectrometer. Preparative high-performance LC was carried out on a Waters Associates LC system 500, and analytical high-performance LC was carried out on a Waters Associates instrument using 3.9 mm i.d. × 30 cm μBondapak C_{18} column. GLC, high-performance LC, and mass spectral data were provided courtesy of the Fritzsche, Dodge and Olcott, Inc., Instrumental Laboratory.

Elemental microanalyses were performed by Childers Laboratories, Milford, NJ. Melting points were determined with a Thomas Model 40 micro hot-stage apparatus and are uncorrected.

Ritter Reaction of Lactones 6. γ-Lactone **6** (13.77 g, 71.0 mmol) was added portionwise to concentrated sulfuric acid (280 mL) at −10 °C. Acetonitrile (2.91 g, 71.0 mmol) was added during 30 min while the reaction temperature was maintained between −5 and −10 °C, and additional acetonitrile (2.91 g) was then added during 1 h. After being stirred for 15 min, the solution was poured into 2 L of ice and extracted with chloroform/2-propanol (85:15) (8 × 80 mL). The organic layers were washed with 10% NaOH (3 × 30 mL), the basic extracts were washed with chloroform/2-propanol (1 × 20 mL), and the combined organic extracts were dried (Na_2SO_4). Evaporation of the solvents gave 4.55 g (33%) of a mixture of lactones **6**, **31**, and **7** in a ratio of 48:11:41. The basic extracts from above were cooled to 0 °C, acidified with 40% sulfuric acid, and extracted with chloroform/2-propanol (85:15) (5 × 50 mL). The extracts were dried (Na_2SO_4) and the solvents evaporated to give 11.67 g (65%) of a colorless solid.

A mixture of the acids from above (11.67 g, 46.1 mmol), *p*-toluenesulfonic acid (0.397 g, 2.31 mmol), and ethanol (250 mL) was heated at reflux, using a Soxhlet extractor containing 3-Å molecular sieves. After 30 h the solution was cooled and concentrated, and the residue was dissolved in chloroform (100 mL). The solution was washed with saturated $NaHCO_3$ (3 × 20 mL) and dried (Na_2SO_4). Evaporation of the solvent gave 12.10 g (94%, 61% based on lactone **6**) of a viscous oil. A sample of this oil (0.168 g, 0.6 mmol) was reacted with *p*-toluenesulfonyl chloride (0.228 g, 1.2 mmol) and pyridine (9 mL), as described below for the preparation of ester **21**, to give 0.109 g (82%) of a mixture of esters. GLC analysis indicated 61% **21**, 21% **28**, 11% **29**, and 7% **22**.

Purification of Ritter Adducts. Ethyl 3-(*syn*-1,7-Dimethyl-2-(acetylamino)bicyclo[2.2.1]hept-7-yl)propanoate (18).[5] The mixture of amide esters (11.93 g, obtained from the Ritter reaction described above) was chromatographed in two portions on a Waters Prep Pak 500/C_{18} (eluant: methanol/water, 65:35). Combination of the appropriate fractions and evaporation of the solvents gave 7.50 g of a white solid (mp 83–84 °C). Crystallization from petroleum ether (bp 30–60 °C)/ethyl acetate gave 5.96 g of amide ester **18**: mp 85–86 °C (one peak by analytical high-performance LC); NMR ($CDCl_3$) δ 0.89 (6 H, s, 2 >CCH_3), 1.13–1.37 (3 H, t, J = 7 Hz, CH_2CH_3), 1.95 (3 H, s, $COCH_3$), 0.9–2.5 (11 H, m), 3.7–4.2 (1 H, m, >CHNH), 3.97–4.32 (2 H, q, J = 7 Hz, CH_2CH_3), 5.1–5.8 (1 H, br s, NH); IR ($CHCl_3$) 3440, 2960, 1725, 1670 cm^{-1}; mass spectrum *m/e* 281, 236, 223, 217, 194. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.37; H, 9.49; N, 5.06.

Ethyl 3-(*anti*-1,7-Dimethyl-2-(acetylamino)bicyclo[2.2.1]hept-7-yl)propanoate (19).[5] Further chromatographic purification of other fractions from above gave an oil which crystallized upon standing. Recrystallization from petroleum ether (bp 30–60 °C)/ethyl acetate gave **19**: mp 63–64 °C (one peak by analytical high-performance LC); NMR ($CDCl_3$) δ 0.83 (3 H, s, >CCH_3), 0.87 (3 H, s, >CCH_3), 1.15–1.38 (3 H, t, J = 7 Hz, CH_2CH_3), 0.9–2.5 (11 H, m), 1.98 (3 H, s, $COCH_3$), 3.8–4.3 (1 H, m, >CHNH), 3.97–4.33 (2 H, q, J = 7 Hz, CH_2CH_3), 5.5–6.2 (1 H, br s, NH); IR ($CDCl_3$) 3450, 2960, 1725, 1670 cm^{-1}; mass spectrum *m/e* 281, 238, 222, 217, 194, 181. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.41; H, 9.62; N, 4.89.

Ethyl 3-(7,7-Dimethyl-2-(acetylamino)bicyclo[2.2.1]hept-1-yl)propanoate (20).[5] Further chromatographic purification of other fractions from the purification of **18** gave a colorless oil which did not crystallize (one peak by analytical high-performance LC): NMR ($CDCl_3$) δ 0.87 (3 H, s, *anti*-7-CH_3), 0.97 (3 H, s, *syn*-7-CH_3), 1.13–1.37 (3 H, t, J = 7 Hz, CH_2CH_3), 0.9–2.6 (11 H, m), 1.97 (3 H, s, $COCH_3$), 3.7–4.3 (1 H, m, >CHNH), 3.95–4.30 (2 H, q, J = 7 Hz, CH_2CH_3), 5.6–6.2 (1 H, br s, NH); IR (film) 3300, 2960, 1725, 1660 cm^{-1}; mass spectrum, *m/e* 281, 266, 238, 222, 208, 194. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 67.77; H, 9.78; N, 4.86.

Ethyl 3-(2-*exo*-Methyl-3-methylenebicyclo[2.2.1]hept-2-yl)propanoate (21). A mixture of amide **18** (10.50 g, 37.4 mmol,

(8) Corey, E. J.; Yamamoto, H. *J. Am. Chem. Soc.* **1970**, *92*, 226.
(9) Klein, E.; Rojahn, W. 6th International Congress of Essential Oils, San Francisco, CA, Sept 12, 1974, Paper No. 163.

mp 85–86 °C), *p*-toluenesulfonyl chloride (14.25 g, 74.7 mmol), and pyridine (375 mL) was heated at reflux for 18 h. The dark-colored mixture was cooled, poured into water (900 mL), and extracted with ether (6 × 100 mL). The extracts were washed successively with water (2 × 50 mL), 2 N hydrochloric acid (5 × 50 mL), water (2 × 50 mL), and saturated $NaHCO_3$ (2 × 50 mL) and dried ($MgSO_4$). Evaporation of solvent and distillation of the residue through a short-path column gave 7.70 g (93%) of ester **21**, bp 89–91 °C (0.5 mm). GLC analysis indicated 92% **21** and 8% **22**. Distillation of the above material through a spinning-band column gave a fraction (3.65 g) which was 99% pure by GLC: NMR ($CDCl_3$) δ 0.99 (3 H, s, $>CCH_3$), 1.13–1.38 (3 H, t, J = 7 Hz, CH_2CH_3), 1.0–2.5 (11 H, m), 2.57–2.80 (1 H, m, $CHC{=}CH_2$), 3.95–4.30 (2 H, q, J = 7 Hz, CH_2CH_3), 4.52 and 4.78 (2 H, 2 s, $>C{=}CH_2$); IR (film) 2950, 1735, 1660 cm^{-1}; mass spectrum, *m/e* 222, 207, 194, 193, 147, 134. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.98. Found: C, 75.48; H, 9.84.

Ethyl 3-(1,7-Dimethyltricyclo[2.2.1.$0^{2,6}$]hept-7-yl)-propanoate (22). *m*-Chloroperbenzoic acid (1.208 g, 5.95 mmol, 85% pure) was added portionwise to a mixture of $NaHCO_3$ (0.882 g, 10.5 mmol) and esters **22** and **21** (1.554 g, 7 mmol, an intermediate fraction from the distillation of ester **21**, containing 28% **22** and 66% **21**) in methylene chloride (70 mL) and water (21 mL). The mixture was stirred vigorously for 2.5 h and the layers were separated. The aqueous layer was extracted with methylene chloride (2 × 10 mL). The combined organic layers were washed with 1 N NaOH (3 × 10 mL) and then water (2 × 10 mL) and dried (Na_2SO_4). The solvents were evaporated and the residue was chromatographed on silica gel to give, after evaporation of solvent and kugelrohr distillation, 0.405 g of an oil, bp 100–110° C (3 mm), which according to GLC analysis contained 87% **22** and 9% **21**. Repeating this process with 0.271 g of this mixture of **22** and **21** gave 0.217 g of ester **22**.[10] GLC analysis indicated a purity of 95%: NMR (CCl_4) δ 0.82 (5 H, s, cyclopropyl CH_3 and 2 H), 1.03 (3 H, s, CH_3), 1.12–1.35 (3 H, t, J = 7 Hz, CH_2CH_3), 0.9–2.4 (9 H, m), 3.88–4.23 (2 H, q, J = 7 Hz, CH_2CH_3); IR (film) 2960, 1730 cm^{-1}; mass spectrum, (*m/e*) 222, 207, 179, 161. Spectral data for the corresponding methyl ester has been reported.[11]

7-(4-Methyl-3-pentenyl)-1,7-dimethyltricyclo[2.2.1.$0^{2,6}$]-heptane (α-Santalene) (3). A solution of ester **22** (0.181 g, 0.815 mmol) in toluene (10 mL) was cooled to −78 °C, and diisobutylaluminum hydride (1 mL of a 1 M hexane solution) was added dropwise during 5 min. After being stirred at −78 °C for 3.5 h, the solution was poured into 5% acetic acid (7 mL) and stirred vigorously. The aqueous layer was extracted with toluene (4 × 5 mL). The organic extracts were washed with saturated $NaHCO_3$ (5 × 5 mL) and dried (Na_2SO_4), and the solvent was evaporated. Kugelrohr distillation of the residue gave 0.140 g of aldehyde **24**: NMR ($CDCl_3$) δ 0.84 (3 H, s, cyclopropyl CH_3), 0.86 (2 H, s, cyclopropyl 2 H), 1.02 (3 H, s, $>CCH_3$), 0.9–2.4 (9 H, m), 9.73–9.81 (1 H, t, J = 2 Hz, CHO).

To a suspension of isopropyltriphenylphosphonium iodide (0.375 g, 0.866 mmol) in dimethoxyethane (4 mL) cooled to 0 °C was added *n*-butyllithium (0.35 mL of a 2.45 M hexane solution, 0.86 mmol). After the solution was stirred for 10 min, aldehyde **24** (0.140 g, 0.787 mmol, from above) in dimethoxyethane (2 mL) was added. After being stirred for 17 h, the mixture was poured into water (15 mL) and extracted with petroleum ether (bp 35–60 °C) (4 × 10 mL). The extracts were washed with water (3 × 5 mL) and brine (5 mL) and dried (Na_2SO_4), and the solvents were evaporated. Most of the triphenylphosphine oxide was removed by crystallization from petroleum ether (bp 35–60 °C). Evaporation of the filtrate and kugelrohr distillation of the residue gave 0.176 g of a colorless oil, bp 100–110 °C (5 mm). GLC analysis indicates one major component (87%), with a retention time corresponding to that of α-santalene (**3**) (isolated from East Indian sandalwood oil). Chromatography and kugelrohr distillation gave material which according to GLC analysis was 97% pure: NMR (CCl_4) δ 0.82 (5 H, s, cyclopropyl CH_3 and 2 H), 0.98 (3 H, s, $>CCH_3$), 1.58 and 1.65 (6 H, 2 s, $CH{=}C(CH_3)_2$), 0.9–2.20 (7 H, m), 2.3–2.6 (2 H, m, $CH_2CH{=}C(CH_3)_2$), 4.85–5.15 (1 H, m, $CH{=}C(CH_3)_2$); IR (film) 3050, 2960, 1670, 1455 cm^{-1}; mass spectrum *m/e* 204, 181, 179, 161 (lit.[4]).

Retro-Ritter Reaction of Amide 19. A mixture of amide **19** (0.168 g, 0.6 mmol, mp 63–64 °C), *p*-toluenesulfonyl chloride (0.228 g, 1.2 mmol), and pyridine (9 mL) was heated at gentle reflux for 19 h. The mixture was cooled, poured into water (25 mL), and extracted with ether (5 × 15 mL). The extracts were washed with water (2 × 10 mL), 2 N HCl (6 × 10 mL), water (2 × 10 mL), and saturated $NaHCO_3$ (2 × 10 mL) and dried ($MgSO_4$). The solvents were evaporated and the residue was dissolved in petroleum ether (bp 35–60 °C) and filtered through silica gel (0.2 g). Evaporation of solvent and kugelrohr distillation gave 0.115 g (86% yield) of a colorless oil, bp 100–110 °C (3 mm). GLC analysis indicated 9% ester **22** and 88% ester **28**.[1]

Retro-Ritter Reaction of Amide 20. A mixture of amide **20** (0.110 g, 0.391 mmol, pure by analytical high-performance LC), *p*-toluenesulfonyl chloride (0.149 g, 0.782 mmol), and pyridine (8 mL) was heated at gentle reflux for 18 h. Workup as described above gave 0.073 g (84% yield) of a colorless oil, bp 100–110 °C. GLC analysis indicated 79% ester **29**[1] and 3% each of esters **21** and **28**. None of the ester **22** was observed.

3-(2-*exo*-Methyl-3-methylenebicyclo[2.2.1]hept-2-yl)-propanal (23). A solution of ester **21** (0.888 g, 4 mmol) in toluene (50 mL) was cooled to −78 °C and diisobutylaluminum hydride (5.0 mL of a 1 M hexane solution) was added dropwise during 5 min. After being stirred at −78 °C for 3.5 h, the solution was poured into 5% acetic acid (30 mL) and stirred vigorously. The aqueous layer was extracted with toluene (3 × 10 mL). The combined organic layers were washed with saturated $NaHCO_3$ (4 × 10 mL) and dried (Na_2SO_4), and the solvent was evaporated. Kugelrohr distillation of the residue gave 0.646 g (91%) of aldehyde **23**, bp 75–85 °C (1 mm). GLC analysis indicated one major component (94%): NMR ($CDCl_3$) δ 1.00 (3 H, 2 s, CH_3), 1.0–2.6 (11 H, m), 2.60–2.83 (1 H, m, $CHC{=}CH_2$), 4.54–4.82 (2 H, 2 s, $C{=}CH_2$), 9.80–9.86 (1 H, t, J = 2 Hz, CHO); IR (film) 2960, 2700, 1725, 1655 cm^{-1}; mass spectrum, *m/e* 178, 160, 145; semicarbazone, mp 180.5–182 °C (semicarbazone of the exo aldehyde, mp 167–168.5[1]). Anal. Calcd for $C_{13}H_{21}N_3O$: C, 66.35; H, 9.00; N, 17.87. Found: C, 66.33; H, 8.84; N, 17.54.

2-*exo*-Methyl-2-*endo*-(4-methyl-3-pentenyl)-3-methylenebicyclo[2.2.1]heptane (Epi-β-santalene) (8). To a suspension of isopropyltriphenylphosphonium iodide (1.520 g, 3.52 mmol) in tetrahydrofuran (30 mL) at 0 °C was added dropwise *n*-butyllithium (1.44 mL of a 2.45 M hexane solution, 3.52 mmol). The solution was stirred for 10 min at 0 °C and then aldehyde **23** (0.626 g, 3.52 mmol, 94% pure) in tetrahydrofuran (5 mL) was added dropwise. After being stirred for 18 h at 25 °C, the mixture was poured into water (70 mL) and extracted with petroleum ether (bp 35–60 °C, 4 × 15 mL). The extracts were washed with water (3 × 10 mL) and brine (10 mL) and dried (Na_2SO_4). The solvent was evaporated and most of the triphenylphosphine oxide was removed by crystallizing the residue from petroleum ether (bp 35–60 °C). Evaporation of the mother liquor and kugelrohr distillation of the residue gave 0.544 g (76%) of epi-β-santalene (**8**), bp 105–110 °C (5 mm). GLC analysis indicated one major component (96%): NMR (CCl_4) δ 1.02 (3 H, s, CH_3), 1.0–2.2 (11 H, m), 1.61 and 1.66 (6 H, 2 s, $CH{=}C(CH_3)_2$), 2.54–2.76 (1 H, m, $CHC{=}CH_2$), 4.43 and 4.67 (2 H, 2 s, $C{=}CH_2$), 4.80–5.27 (1 H, m, $CH{=}C<$); IR (film) 2960, 1660, 1470, 1460 cm^{-1}; mass spectrum *m/e* 204, 189, 161, 122, 94. A sample of a mixture of β-santalene (**4**) and epi-β-santalene (**8**) was isolated from East Indian sandalwood oil by preparative GLC. The 80-MHz ^1H NMR spectrum of the mixture shows the *exo*-methyl group of epi-β-santalene at δ 1.02 and the *endo*-methyl group of β-santalene at δ 1.04, consistent with previously reported spectral data.[4] Comparison of the above spectrum with the spectra of the synthetic material and β-santalene (**4**)[1] confirmed that epi-β-santalene (**8**) had been prepared.

(*Z*)-2-Methyl-5-(2-*exo*-methyl-3-methylenebicyclo[2.2.1]-hept-2-yl)-2-penten-1-ol (Epi-*cis*-β-santalol) (9). To a suspension of ethyltriphenylphosphonium bromide (2.037 g, 5.49 mmol) in tetrahydrofuran (15 mL) at 0 °C was added *n*-butyllithium (2.2 mL of a 2.45 M hexane solution, 5.4 mmol). After being stirred for 20 min, the solution was cooled to −78 °C and aldehyde **23** (0.814 g, 4.57 mmol, 96% pure) in tetrahydrofuran (4 mL) was added dropwise during 5 min. After being stirred for 5 min, *n*-butyllithium (2.8 mL of a 2.45 M hexane solution, 6.86

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mmol) was added dropwise during 10 min and the solution was stirred at −78 °C for 20 min. The solution temperature was adjusted to 0 °C (ice/water bath) and gaseous formaldehyde (generated by heating paraformaldehyde to 150–160 °C in a stream of nitrogen and dried by passing over phosphorus pentoxide) was bubbled into the solution until a straw-colored solution was obtained. The solution was stirred overnight at room temperature and was then poured into saturated ammonium chloride solution (50 mL) and extracted with ether (5 × 10 mL). The ether extracts were washed with water (10 mL), saturated $NaHCO_3$ (2 × 10 mL), and brine (10 mL) and dried ($MgSO_4$). Evaporation of solvents gave 2.39 g of residue, which was chromatographed on silica gel to give, after evaporation of solvent and kugelrohr distillation, 0.339 g (34%) of epi-*cis*-β-santalol (**9**), bp 110–120 °C (0.3 mm), 91% pure. Further purification gave material which was 96% pure: NMR ($CDCl_3$) δ 1.01 (3 H, s, $>CCH_3$), 1.79 (3 H, br s, $=C(CH_2OH)CH_3$), 1.0–2.3 (12 H, m), 2.60–2.75 (1 H, m, $CHC=CH_2$), 4.14 (2 H, s, CH_2OH), 4.46 and 4.73 (2 H, 2 s, $>C=CH_2$), 5.15–5.35 (1 H, m, $CH=C<$); IR (film) 3330, 2940, 1660 cm^{-1}; mass spectrum, *m/e* 220, 202, 187, 159. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.48; H, 10.91.

(*E*)-Ethyl 2-Methyl-5-(2-*exo*-methyl-3-methylenebicyclo[2.2.1]hept-2-yl)-2-pentenoate (30). Sodium hydride (0.212 g of a 50% oil dispersion, 4.42 mmol) was washed with dimethoxyethane (3 × 5 mL). To a suspension of the sodium hydride in dimethoxyethane (25 mL) was added triethyl phosphonopropanoate (1.052 g, 4.42 mmol) in dimethoxyethane (5 mL). When hydrogen evolution had ceased, the solution was cooled (0 °C) and aldehyde **23** (0.786 g, 4.42 mmol, 86% pure) in dimethoxyethane (5 mL) added dropwise during 5 min. The mixture was stirred at 25 °C for 1 h, then heated at 60–70 °C for 30 min, cooled, poured into water (30 mL), and extracted with ether (4 × 10 mL). The ether extracts were washed with water (3 × 10 mL) and then brine (10 mL) and dried ($MgSO_4$). The solvents were evaporated and the residue was chromatographed on silica gel to give, after evaporation of solvent and kugelrohr distillation, 0.773 g (67%) of esters, bp 110–115 °C (0.3 mm). GLC analysis indicated 81% *E* and 9% *Z* ester **30**: NMR ($CDCl_3$) δ 1.03 (3 H, s, $>CCH_3$), 1.15–1.38 (3 H, t, J = 7 Hz, CH_2CH_3), 1.85 (3 H, br s, $=C(CO_2R)CH_3$), 1.0–2.4 (11 H, m), 2.6–2.8 (1 H, m, $CHC=CH_2$), 4.00–4.37 (2 H, q, J = 7 Hz, CH_2CH_3), 4.48 and 4.73 (2 H, 2 s, $>C=CH_2$), 6.6–7.0 (1 H, m, $CH=C(CO_2R)$); IR (film) 2960, 1705, 1650, 1460 cm^{-1}; mass spectrum, *m/e* 262, 247, 234, 216, 189, 161; UV (95% EtOH) 217 nm (calcd 217) (ε 16 300). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.81; H, 9.98. Found: C, 77.58; H, 10.10.

(*E*)-2-Methyl-5-(2-*exo*-methyl-3-methylenebicyclo[2.2.1]hept-2-yl)-2-penten-1-ol (Epi-*trans*-β-santalol) (10). To a cold (0 °C) solution of aluminum chloride (0.089 g, 0.67 mmol) in ether (10 mL) was added portionwise lithium aluminum hydride (0.076 g, 2 mmol). The solution was stirred for 30 min at 0 °C and then esters **30** (0.262 g, 1 mmol; 82% *E*, 14% *Z*) in ether (3 mL) were added dropwise. The solution was stirred at 0 °C for 1.3 h and then cautiously poured into 2 N HCl (5 mL) and ice (5 mL). The aqueous layer was extracted with ether (4 × 10 mL). The combined organic extracts were washed successively with water (2 × 5 mL), saturated $NaHCO_3$ (3 × 5 mL), and brine (5 mL) and dried ($MgSO_4$). Evaporation of solvent and kugelrohr distillation gave 0.191 g (87%) of a colorless oil, bp 120–130 °C (0.3 mm). GLC analysis indicated 83% epi-*trans*-β-santalol (**10**) and 14% epi-*cis*-β-santalol (**9**). A sample for 80-MHz ^1H NMR analysis was obtained by preparative GLC: NMR ($CDCl_3$) δ 1.03 (3 H, s, $>CCH_3$), 1.69 (3 H, br s, $=C(CH_2OH)CH_3$), 1.0–2.3 (12 H, m), 2.60–2.75 (1 H, m, $CHC=CH_2$), 4.00 (2 H, s, CH_2OH), 4.47 and 4.72 (2 H, 2 s, $>C=CH_2$), 5.3–5.6 (1 H, m, $CH=C(CH_2OH)$); IR (film) 3300, 2960, 1660 cm^{-1}; mass spectrum, *m/e* 220, 205, 202, 187, 159. Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.61; H, 10.95.

2-Methyl-5-(2-*exo*-methyl-3-methylenebicyclo[2.2.1]hept-2-yl)pentan-1-ol (Dihydroepi-β-santalol) (11). Lithium shot was added to a mixture of esters **30** (0.262 g, 1 mmol), ethanol (5 mL), ether (5 mL), and ammonia (20 mL) until a persistent blue color was observed. Ammonium chloride (2 g) was added and ammonia allowed to evaporate. The residue was dissolved in ether (20 mL) and water (10 mL). The aqueous layer was extracted with ether (3 × 5 mL), and the ether extracts were washed successively with water (2 × 5 mL) and brine (5 mL) and dried ($MgSO_4$). The solvents were evaporated and the residue was chromatographed on silica gel to give after kugelrohr distillation 0.155 g (70%) of a colorless oil, bp 110–130 °C (0.3 mm). GLC analysis indicated a purity of 99%: NMR (CCl_4) δ 0.84–0.96 (3 H, d, J = 7 Hz, $>CHCH_3$), 0.99 (3 H, s, CH_3), 0.8–2.2 (14 H, m), 2.63 (1 H, s, OH), 2.5–2.75 (1 H, m, $CHC=CH_2$), 3.33–3.42 (2 H, d, J = 6 Hz, CH_2OH), 4.42 and 4.66 (2 H, 2 s, $>C=CH_2$); IR (film) 3350, 2960, 1660 cm^{-1}; mass spectrum, *m/e* 222, 207, 204, 161, 149. Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.62; H, 11.57.

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Synthesis of *prox*-Benzoisoallopurinol

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Pyrazolo[3,4-*f*]quinazolin-9-one (*prox*-benzoisoallopurinol, **1**), an extended analogue of 7-hydroxypyrazolo[4,3-*d*]pyrimidine (isoallopurinol, **2**) and a potential dimensional probe for substrates of xanthine oxidase, has been synthesized by two independent routes. The title compound, prepared by elaboration of either a suitably substituted indazole or a quinazolinone, was found to be an active substrate for and an alternative-substrate inhibitor of xanthine oxidase. The product of enzymatic oxidation of *prox*-benzoisoallopurinol has been identified as the corresponding *prox*-benzoisoalloxanthine.

Recent work in this laboratory has centered on the synthesis of "stretched-out" versions of biologically active purine compounds.[1] Encouraged by the fluorescence and biochemical properties of extended analogues in this se-

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