τ 4.4–5.2 region were superimposable with the corresponding ones of the 6-ethoxycarbonyl compound **9**.

Anal. Calcd for $C_{13}H_{19}NO_{10}$: C, 44.70; H, 5.48; N, 4.01. Found: C, 44.68; H, 5.39; N, 3.88.

Acid-catalyzed hydrolysis of the ethoxycarbonyl group in **9** could be effected, though rather retardedly, by refluxing sirup B with a strongly acidic ion exchange resin (Merck I) in methanol. As monitored by tlc (1:1 benzene–ethyl acetate) the reaction was still incomplete after 5 days, giving after work-up and acetylation as performed above, a tri-*O*-acetate in very low yield (3%), identical in all respects with **13**.

Methyl 3-Amino-3-deoxy-6-*O*-ethoxycarbonyl-α-D-glucopyranoside (10).—Sirup B (900 mg, 3.0 mmol) in 80 ml of ethanol was hydrogenated in the presence of 5 ml of Raney nickel T4 catalyst[22] for 3 hr at 100 atm. Removal of the catalyst followed by evaporation to dryness afforded a solid residue, which was chromatographically not homogeneous. After two recrystallizations from ethyl acetate, 200 mg (25%) of **10** was obtained as colorless crystals: mp 122–125° (reported[7] for alleged **3** mp 128.5–129.5°); nmr (D_2O) τ 5.24 (d, 1, $J_{1,2}$ = 3.5 Hz, H-1), 5.55 (m, 2, C-6 CH_2), 5.76 (q, 2, J = 7 Hz, $EtCH_2$), 6.15 (m, 1, H-5), 6.51 (q, 1, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10 Hz, H-2), 6.59 (s, 3, OCH_3), 6.68 (t, 1, $J_{3,4} = J_{4,5}$ = 10 Hz, H-4), 7.05 (t, 1, H-3), 8.73 (t, 3, $EtCH_3$).

Anal. Calcd for $C_{10}H_{19}NO_7$: C, 45.28; H, 7.22; N, 5.28. Found: C, 45.12; H, 7.10; N, 5.35.

Methyl 3-Acetamido-3-deoxy-2,4-di-*O*-acetyl-6-*O*-ethoxycarbonyl-α-D-glucopyranoside (12).—To a prehydrogenated suspension of platinum (1 g) in 1:1 methanol–acetic anhydride (40 ml) was added 420 mg of nitrodi-*O*-acetate **9**, and the hydrogenation was continued in an autoclave at 100 atm of H_2 for 2 hr. Removal of the catalyst, which was thoroughly washed with methanol, and concentration of the combined filtrate and washings *in vacuo*, followed by repeated reevaporations from benzene, left a crystalline residue, which was filtered off (440 mg, quantitative). The crude product was recrystallized twice from ethanol to give 170 mg (40%) of **12** as colorless crystals: mp 179°; $[\alpha]^{23}D$ +102° (c 1, $CHCl_3$) [reported for alleged **5**[7] mp 177–178° from 2-propanol and $[\alpha]^{25}D$ +119° (c 1.1, $CHCl_3$)]; nmr (DMSO-d_6) τ 2.21 (d, 1, $J_{3,NH}$ = 9 Hz, NH), 5.1–5.4 (complex m, 3, H-1, H-2, and H-4), 5.7–6.2 (m, 6, H-3, H-5, C-6 CH_2 and $EtCH_2$), 6.66 (s, 3, OCH_3), 8.01 and 8.04 (s, 3, C-2 and C-4 OAc), 8.27 (s, 3, NHAc), 8.78 (t, 3, J = 7 Hz, $EtCH_3$).

Anal. Calcd for $C_{16}H_{25}NO_{10}$: C, 48.86; H, 6.41; N, 3.58. Found: C, 49.02; H, 6.55; N, 3.42.

Overnight treatment of the aminoglycoside **10** with pyridine–acetic anhydride at room temperature similarly afforded a triacetate, identical in all respects with **12**, as obtained above.

Methyl 3-Acetamido-3-deoxy-2,4,6-tri-*O*-acetyl-α-D-glucopyranoside (14).—A solution of 300 mg of triacetyl glucoside **12** in 20 ml of methanolic ammonia was kept at room temperature overnight, and subsequently taken to dryness with repeated reevaporations from methanol. The sirupy residue was dissolved in 2:1 pyridine–acetic anhydride (15 ml), and the resulting solution was kept overnight and then evaporated to dryness *in vacuo*. Several reevaporations from benzene and treatment with activated carbon in the same solvent left a residue on evaporation which crystallized on trituration with ethanol. Recrystallization from ethanol afforded 180 mg (65%) of **14**: mp 178–179°; $[\alpha]^{23}D$ +105° (c 1, $CHCl_3$) (mp 178–179°, $[\alpha]^{23}D$ +109°, reported previously[11]); nmr (DMSO-d_6) τ 2.23 (d, 1, $J_{3,NH}$ = 9 Hz, NH), 5.2 (m, 3 H-1, H-2, and H-4), 5.73 (broad m, 1, H-3), 5.96 (m, 3, H-5 and C-6 CH_2), 6.67 (s, 3, OCH_3), 8.00, 8.01, and 8.03 (s, 3, C-2, C-4, and C-6 OAc), 8.25 (s, 3, NHAc).

Anal. Calcd for $C_{15}H_{23}NO_9$: C, 49.86; H, 6.42; N, 3.88. Found: C, 49.97; H, 6.25; N, 3.61.

Registry No.—**8**, 34246-31-6; **8** manno derivative, 34280-29-0; **9**, 34246-26-9; **10**, 34246-27-0; **12**, 34280, 30-3; **13**, 34246-28-1; **14**, 2595-38-2.

(22) S. Nishimura, *Bull. Chem. Soc. Jap.*, **32**, 61 (1959).

Studies Related to the Synthesis of (±)-Dihydro-β-santalol[1]

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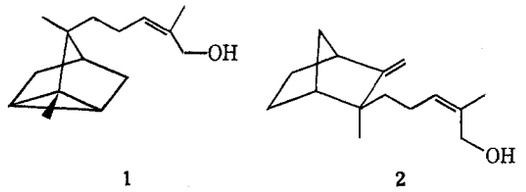
Several related schemes for the synthesis of the novel sesquiterpene dihydro-β-santalol (**3**), a material possessing the powerful, woody fragrance of East Indian sandalwood oil, are described. A preferred sequence utilizes boric acid esters as a means of protecting reactive hydroxyl groups during hydrobromination, alkylation, and Wittig reactions. A novel Meerwein–Ponndorf–Verley reduction discovered during these synthetic studies is also described.

East Indian sandalwood oil, an isolate of *Santalum album L.*, is a prized essential oil known for its powerful, sweet woody fragrance.[2] Although numerous minor components are important for the reproduction of the natural aroma of the oil, the two major components—α-santalol (**1**) and β-santalol (**2**)—are responsible for the basic sandalwood note. While syntheses of these two materials have been accomplished,[3] these schemes do not permit the accumulation of large amounts of material owing to the complexity of the natural sesquiterpene structures. The greater synthetic accessibility of compounds in the β series and the challenge to construct a simpler molecule with a powerful sandalwood note prompted us to synthesize dihydro-β-santalol (**3**).



1 **2**

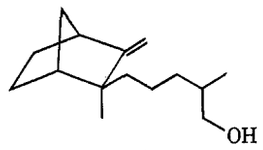
Corey has shown[4] that either of the epimeric methylnorcamphors **4** or **5** undergoes stereoselective alkylation from the exo face to produce 3-*exo*-alkyl-3-*endo*-methylnorcamphors. Using this information, our synthetic scheme was to preconstruct a side chain—such as **6**—which on condensation with ketone **4** or **5** would be expected to yield stereoselectively a dihydro-β-santalol

(1) For a preliminary communication of this work, see W. I. Fanta and W. F. Erman, *Tetrahedron Lett.*, 4155 (1969).

(2) (a) E. Guenther, "The Essential Oils," Vol. V, Van Nostrand, Princeton, N. J., 1952, pp 173–186; (b) J. L. Simonsen and D. H. R. Barton, "The Terpenes," 2nd ed, Vol. 3, University Press, Cambridge, England, 1951, pp 98, 178–188; (c) F. V. Wells, *Soap Chem. Spec.*, **43** (12), 74, 76–78, 149–151 (1967).

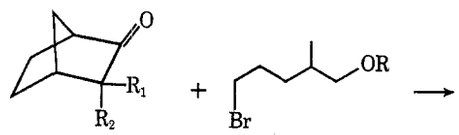
(3) (a) R. G. Lewis, D. H. Gustafson, and W. F. Erman, *Tetrahedron Lett.*, 401 (1967); (b) S. Y. Kamat, K. K. Chakravarti, and S. C. Bhattacharyya, *Tetrahedron*, **23**, 4487 (1967); (c) H. C. Kretschmar and W. F. Erman, *Tetrahedron Lett.*, 41 (1970); (d) J. Colonge, G. Descotes, Y. Bahurel, and A. Menet, *Bull. Soc. Chim. Fr.*, 374 (1966); (e) E. J. Corey, H. A. Kirst, and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **92**, 6314 (1970); (f) E. J. Corey and H. Yamamoto, *ibid.*, **92**, 226 (1970).

(4) E. J. Corey, R. Hartmann, and P. A. Vatakencherry, *ibid.*, **84**, 2611 (1962).



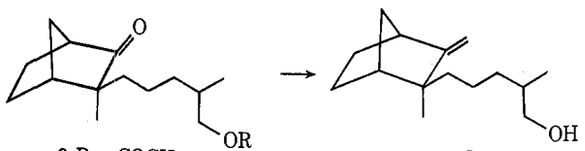
3

precursor such as **9**.[5] Introduction of a methylene function and removal of the alcohol blocking group would yield the synthetic goal **3**.



4, $R_1 = CH_3$; $R_2 = H$
5, $R_1 = H$; $R_2 = CH_3$

6, R = $COCH_3$
7, R = THP
8, R = H

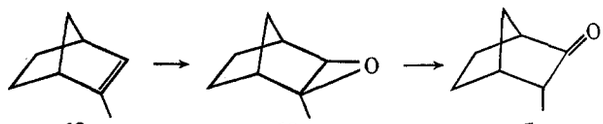


9, R = $COCH_3$
10, R = THP
11, R = H

3

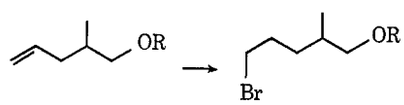
The construction of **3**-*exo*-methylnorcamphor (**4**) can be accomplished through the alkylation of norcamphor as described by Corey.[4] We chose to examine an alternate preparative scheme to 3-methylnorcamphor which we felt would more conveniently allow preparation of large quantities of the required ketone from readily available starting materials. The olefin, 2-methylbicyclo[2.2.1]hept-2-ene (**12**), available in quantity through Diels–Alder condensation of methylcyclopentadiene and ethylene,[6a] offered promise as a precursor to 3-methylnorcamphor. Epoxidation of olefin **12** with *m*-chloroperbenzoic acid[6b] or sodium acetate buffered peracetic acid afforded the exo epoxide **13** in excellent yield.[7] We found that, of the several catalysts examined, boron trifluoride etherate was most efficient and consistent for opening the oxide to methylnorcamphor. This process selectively forms the endo isomer **5**.[8]

With a ready supply of the methylnorcamphor available, we turned our attention to construction of suitable side-chain precursors. Since our intent was to



12 **13** **5**

construct the total side chain prior to its addition to 3-methylnorcamphor, we were interested in the recently reported one-step preparation of 2-methyl-4-pentenol (**14**) by Cherest and coworkers.[9] Although the alcohol had been previously described,[10] this new synthetic scheme offered, more directly, a material ideally suited for simple modifications to side chains such as **6** and **7**.

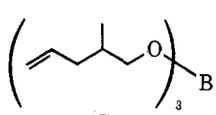


14, R = H
15, R = $COCH_3$
16, R = THP

6, R = $COCH_3$
7, R = THP

Our attention was next directed toward the reactions necessary to convert alcohol **14** into a properly functionalized side-chain precursor. In considering various alcohol blocking groups, we concluded it would be advantageous to employ a group which would protect the alcohol during both a hydrobromination reaction and subsequent combination with methylnorcamphor, and yet be easily removed at a latter stage in the scheme. Some of the problems encountered with the use of standard blocking groups for this multipurpose role are elaborated below.

While the acetate **15** and the tetrahydropyranyl ether **16** were available through standard procedures, the borate **17** proved to be the most versatile in sub-



17

sequent synthetic work. Although borates have been used as blocking groups, extensive use in synthetic organic chemistry has not been described.[11]

Free-radical hydrobromination of unsaturated alcohol **14** offers a simple method for introduction of the desired leaving group. We expected, and subsequently demonstrated experimentally, however, that free-radical hydrobromination of **14** was not practical owing to the inhibitory effect of the free hydroxyl group. We also found that, while the anti-Markovnikov hydrobromination of acetate **15** could be carried out in high yield, attempts to hydrobrominate tetrahydropyranyl ether **16** met with little success. In the latter case, hydrogen abstraction adjacent to the ether oxygen most likely terminates the free-radical process and bromo ether **18** is the only observed product.

Anti-Markovnikov hydrobromination of borate **17**

(5) The alkylation of ketone **4** or **5** with side chains such as **6**, which contain an asymmetric carbon atom, would be expected to produce diastereomeric mixtures. No attempt was made to separate the two diastereomers in products such as **9**, **10**, **11**, and **3**.

(6) (a) K. Alder and H. J. Ache, *Chem. Ber.*, **95**, 503 (1962); (b) H. C. Kretschmar, unpublished observation.

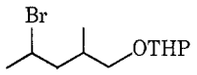
(7) It was anticipated that the epoxidation would occur specifically from the less hindered exo face as has been observed in the epoxidation of bicyclo-[2.2.1]hept-2-ene: H. Kwart and W. G. Vosburgh, *J. Amer. Chem. Soc.*, **76**, 5400 (1954); H. M. Walborsky and D. F. Lonerini, *ibid.*, **76**, 5396 (1954); H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **92**, 6914 (1970).

(8) In the carbonium ion formed by oxide opening, the exo-hydrogen transfer is greatly favored over the endo-hydrogen transfer. As a consequence, the methyl group is oriented endo in the product. For a discussion of methylnorbornyl cation equilibria, see (a) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Ramanick, and D. Houston, *ibid.*, **89**, 2561 (1967); (b) J. A. Berson, A. W. McRowe, R. G. Bergman, and D. Houston, *ibid.*, **89**, 2563 (1967); (c) J. A. Berson and R. G. Bergman, *ibid.*, **89**, 2569 (1967); (d) J. A. Berson, A. W. McRowe, and R. G. Bergman, *ibid.*, **89**, 2573 (1967); (e) J. A. Berson, R. G. Bergman, J. H. Hammons, and A. W. McRowe, *ibid.*, **89**, 2581 (1967); (f) J. A. Berson, J. H. Hammons, A. W. McRowe, R. G. Bergman, A. Remanick, and D. Houston, *ibid.*, **89**, 2590 (1967).

(9) M. Cherest, H. Felkin, C. Frajerman, C. Lion, G. Roussi, and G. Swierczewski, *Tetrahedron Lett.*, 875 (1966).

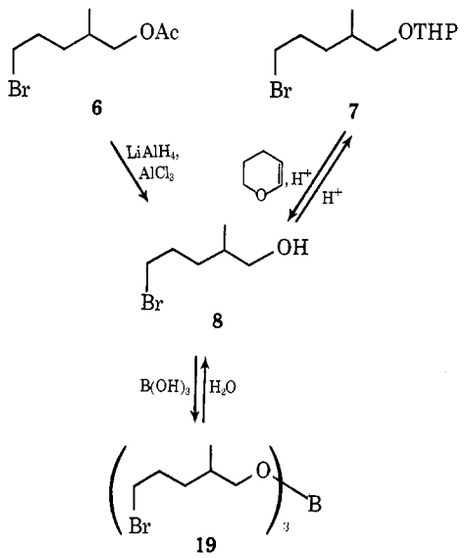
(10) G. I. Fray and N. Polgar, *J. Chem. Soc.*, 2036 (1956).

(11) See J. Staněk, M. Černý, J. Kocourek, and J. Pacák, "The Monosaccharides," Academic Press, New York, N. Y., 1963, pp 40 and 254 and references therein for applications in carbohydrate chemistry. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 64–66 and references therein which describe limited applications in hydroxylation and condensation reactions and in monoglyceride chemistry. W. C. Agosta, *J. Amer. Chem. Soc.*, **89**, 3926 (1967).



18

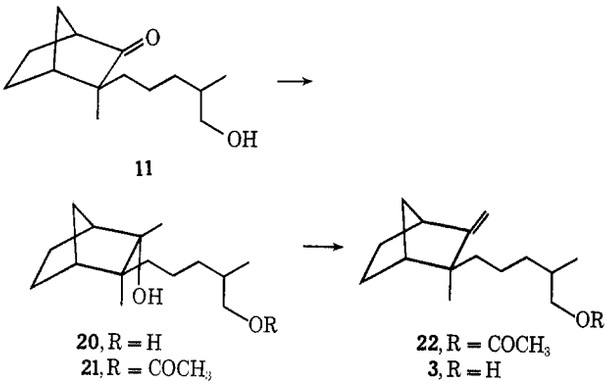
proceeded smoothly and an aqueous isolation procedure afforded directly the bromo alcohol **8**. With these materials available certain interconversions were undertaken which afforded additional compounds for potential use in the remainder of the sequence. For example, while direct saponification of bromo acetate **6** led only to 3-methyltetrahydropyran, reduction with lithium aluminum hydride–aluminum chloride under mild conditions afforded a nearly quantitative yield of bromo alcohol **8**. This material could be converted by standard procedures to the bromo ether **7**. In addition, bromo borate **19** was readily available through interaction of bromo alcohol **8** and boric acid.



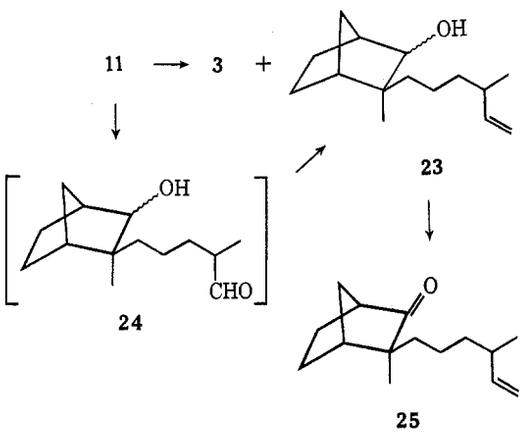
With three potential alkylating agents (**6**, **7**, and **19**) available, we turned our attention to the alkylation of 3-methylnorcamphor. Although an alkylation procedure previously described[4] was used in initial studies, we found that improved yields and product purity resulted when sodium hydride was used in place of sodium amide. We discovered, however, that the readily available bromoacetate **6**, or the corresponding iodoacetate, could not be successfully added to the methylnorcamphor system. While a considerable amount of polymer was formed the major volatile products were identified as starting materials and dehydrohalogenated products such as **15**.

Bromo ether **7**, on the other hand, was smoothly added to methylnorcamphor using either the sodium amide–tetrahydrofuran combination or, preferably, a sodium hydride–benzene system. While the alkylation product **10** could not be effectively purified because of chromatographic instability, we found that removal of the ether blocking group afforded the readily analyzable ketol **11**. This material was also available through alkylation of methylnorcamphor with bromo borate **19**. As noted previously, the borate, being extremely water sensitive, was readily cleaved during an aqueous workup and the ketol **11** was isolated directly in 60–70% yield.

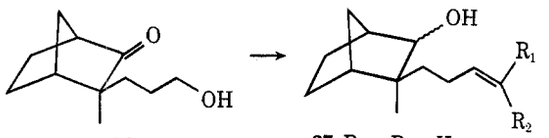
The final conversion (**11** → **3**), which we approached in several different ways, remained to complete the synthesis. Application of Corey's procedure[4] to ketol **11** required certain modifications owing to the side-chain hydroxyl function. Interaction of the ketol **11** with 3 equiv of methyllithium or methylmagnesium bromide followed by monoacetylation of diol **20** afforded hydroxy acetate **21**. Subsequent dehydration to dihydro-β-santalol acetate (**22**) followed by saponification afforded dihydro-β-santalol (**3**) as a colorless viscous oil.



Alternately, one can visualize the use of a Wittig reaction for a more direct conversion of **11** to the desired santalol **3**. We found that condensation of ketol **11** with excess methylenetriphenylphosphorane in dimethyl sulfoxide afforded, in addition to **3**, substantial amounts of a second product. This side product was identified as the isomeric hydroxy olefin **23** which undoubtedly arises from a Wittig reaction on hydroxyaldehyde **24**. (Although an intramolecular Ponndorf–Verley reduction can be recognized as one reasonable pathway for formation of **24**, the actual mechanistic details have not been defined.) The identity of product **23** was further established by oxidation to keto olefin **25** in high yield.



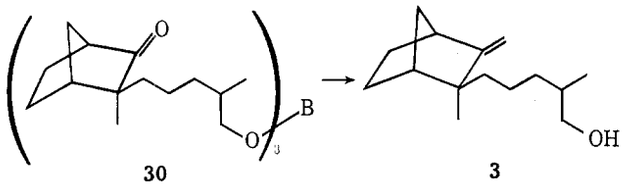
While one can visualize several possible applications in the area of santalol synthesis for this interesting rearrangement, the reaction appears to be quite specific for the methylene Wittig reagent. We attempted to interact ketol **26** with three different Wittig reagents but found that only the simplest would react to give hydroxy olefin **27**. Since neither isopropylidenetriphenylphosphorane nor α-carboethoxyethylidenetriphenylphosphorane could be successfully used, we were unable to gain what initially appeared to be a novel entrance into other santalol systems.



26

27, $R_1 = R_2 = H$
28, $R_1 = R_2 = CH_3$
29, $R = CH_3$; $R = CO_2Et$

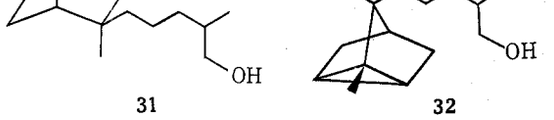
The interaction of the hydroxyl and the keto groups in bicyclic ketol **11** could be circumvented by blocking the hydroxyl as the borate. Subsequent treatment of keto borate **30** with excess methylenetriphenylphosphorane in dimethyl sulfoxide afforded, on hydrolysis, a 90% yield of dihydro-β-santalol (**3**).



30 3

Pure **3** was also obtained directly in high yield from diol **20** using boron trifluoride etherate as a dehydration catalyst. This latter conversion has the advantages of requiring no blocking group, using inexpensive reagents, and proceeding in high yield.

It is of interest at this point to compare the odor properties of dihydro-β-santalol (**3**), tetrahydro-β-santalol (**31**), and dihydro-α-santalol (**32**). Although



31 32

alcohols **31** and **32** have been previously described,[12] we have independently synthesized[13] samples of these materials for direct comparison to dihydro-β-santalol (**3**). While the odor of dihydro-α-santalol is sandalwood in character, it is very much weaker than dihydro-β-santalol. Moreover, the odor of the α isomer is short lived and on dry down the strength is greatly diminished while a sample of dihydro-β-santalol retains its strong and characteristic sandalwood note for an extended period of time. Tetrahydro-β-santalol exhibits a "chemical, earthy, musty" odor and dries down to a very weak, neutral woody odor.[14]

Experimental Section

General.—Ir spectra were recorded on a Perkin-Elmer Model 137 spectrophotometer; nmr spectra were determined with a Varian Model HA-100 spectrometer with chemical shifts measured relative to tetramethylsilane (τ 10) (s, singlet; b s, broad singlet; d, doublet, etc.). Gas–liquid partition chromatography (glpc) was carried out on an Aerograph Model 202B using a flow rate of 100 cc/min on 5 ft × 0.25 in. columns packed with 20% FFAP on 60/80 Chromosorb P column or 20% SE-30 on 60/80 Chromosorb W. The apparatus described by Johnson and Schneider[15] was used to maintain a nitrogen atmosphere. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Boiling points are taken on standard thermometers and are uncorrected.

2-Methylbicyclo[2.2.1]hept-2-ene (12).—Condensation of 80 g (1 mol) of methyl cyclopentadiene dimer with a large excess of ethylene according to the procedure of Alder and Ache[5] and subsequent distillation afforded 38 g (35%) of colorless product, bp 115–117° (lit.[5] bp 117°), which showed 96% purity by glpc analysis.

2-Methyl-*exo*-2,3-epoxybicyclo[2.2.1]heptane (13).—A mixture of 54 g (0.5 mol) of olefin **12** and 60 g (0.75 mol) of sodium acetate in 180 ml of methylene chloride was cooled in an ice bath. The temperature was maintained at 5–10° and 104 ml (0.625 mol) of a 40% peracetic acid solution in acetic acid was added with good stirring over 80 min. The resulting solution was stirred for an additional 10 min and poured into excess 5% aqueous sodium hydroxide, and the layers were separated. The aqueous layer was extracted several times with ether and the combined organic layers were washed with 5% aqueous sodium hydroxide until basic and with brine solution to neutrality and dried ($MgSO_4$). The solvent was evaporated to afford 56.5 g (92%) of epoxide **13** which was suitable for subsequent reactions.

The epoxide could be purified by distillation, bp 95° (100 mm), or preparative glpc[6b] to afford material with the following spectral characteristics: ir (film) 7.6, 8.85, 9.2, 10.0, 10.5, 11.15, 11.6, 11.95 μ; nmr (CCl_4) τ 7.41 (s, 1, C_3 endo H), 8.7 (s, C_2 endo CH_3), 8.4–8.95 (m, CH_2's).

***endo*-3-Methylbicyclo[2.2.1]heptan-2-one (5).**—A solution of 51 g (0.41 mol) of crude epoxide **13** dissolved in 200 ml of benzene was treated, under nitrogen over ~1 min, with 8.3 ml of boron trifluoride etherate. The dark solution was stirred at 60° for 5 hr and cooled slightly, and most of the solvent was removed at reduced pressure. The residual oil, 70.3 g, was distilled to afford 23.7 g (46%) of ketone **5**: bp 80–90° (30 mm); ir (neat) 5.8, 7.7, 8.5, 9.0, 9.6, 10.5 μ; nmr (CCl_4) τ 9.05 (d, 3, J = 7 Hz, $CHCH_3$). The material exhibited greater than 95% purity by glpc.[8]

2-Methyl-4-pentenol (14).—A modification of the procedure of Cherest and coworkers was employed.[9] A solution of 23.2 g (0.4 mol) of allyl alcohol in 60 ml of anhydrous ether was treated with 150 ml of a 3 *M* ethereal methylmagnesium bromide solution (0.45 mol) over a 3–4-hr period. The resulting clear brown solution was subsequently treated in one portion with 360 ml of a 1.4 *M* ethereal allylmagnesium bromide solution and refluxed under nitrogen for 50 hr. The cooled reaction was decomposed by slow addition to ice and solution was subsequently effected by cautious addition of 10% aqueous hydrochloric acid. The solution was saturated with salt, the product was isolated with ether, and the combined extracts were washed with brine and dried ($MgSO_4$). Removal of the solvent and subsequent distillation afforded 25.4 g (64%) of unsaturated alcohol **14**, bp 53–58° (14 mm), which showed 96% purity by glpc.

Material purified by redistillation and glpc exhibited the following physical properties: bp 57–58° (12 mm); $n^{21.5}D$ 1.4319 (lit.[10] $n^{18}D$ 1.4345); ir (neat) 3.00, 3.28, 6.10, 9.68, 10.04, 10.91 μ; nmr (CCl_4) τ 4.00–4.51 (m, 1, -CH=), 4.90–5.20 (m, 2, $CH=CH_2$), 5.60 (s, 1, OH), 6.40–6.80 (m, 2, CH_2OH), 9.10 (d, 3, J = 7 Hz, $CHCH_3$).

Anal. Calcd for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 72.1; H, 12.2.

2-Methyl-4-pentenyl Acetate (15).—A solution of 3.44 g (34.4 mmol) of alcohol **14** in 35 ml of anhydrous pyridine was treated under a nitrogen atmosphere with 10.78 g (10 ml, 100 mmol) of acetic anhydride. The reaction was stirred at room temperature for 24 hr and poured into brine, and the product was isolated with ether. The extracts were washed with 3% aqueous hydrochloric acid and brine and dried ($MgSO_4$). The solvent was removed and the residual crude oil was distilled to afford 4.3 g (88%) of acetate **15**, bp 60–65° (17 mm), which showed 99% purity by glpc.

A sample of the material subjected to redistillation exhibited the following physical properties: bp 54–56° (13 mm), $n^{26}D$ 1.4140; ir (neat) 3.28, 5.71, 6.10, 8.06, 9.62, 10.05, 10.91 μ; nmr (CCl_4) τ 4.10–4.55 (m, 1, -CH=), 4.90–5.19 (m, 2, CH=

(12) V. Herout, V. Jarolím, and J. Plíva, *Chem. Listy*, **50**, 1271 (1956); *Chem. Abstr.*, **51**, 296*de* (1957).

(13) The preparation of dihydro-α-santalol (**32**) was carried out by R. G. Lewis using precursors prepared by R. G. Lewis, D. H. Gustafson, and W. F. Erman, *Tetrahedron Lett.*, 401 (1967). A mixture of *cis*- and *trans*-ethyl-α-santalates was catalytically reduced and the resulting saturated ester was reduced with lithium aluminum hydride to afford the required santalol **32**.

(14) We are indebted to E. J. Matre, W. A. Whitehead, J. B. Dacey, and R. W. Martin, Senior Perfumers of The Procter & Gamble Co., for these odor evaluations.

(15) W. S. Johnson and W. P. Schneider, *Org. Syn.*, **30**, 18 (1950).

CH_2), 6.05–6.36 (m, 2, CH_2O), 8.08 (s, 3, $COCH_3$), 9.11 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.3; H, 10.0.

2-Methyl-4-pentenyl Tetrahydropyranyl Ether (16).—A mixture of 1.4 g (14 mmol) of alcohol **14** and 1.12 g (14 mmol) of dihydropyran was cooled in an ice bath and treated under nitrogen with 5 drops of phosphorus oxychloride. The resulting reaction was stirred at room temperature for 2.5 hr and added to 100 ml of 2% aqueous sodium hydroxide and the product was isolated with ether. The combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed to afford crude product. Subsequent distillation afforded 2.14 g (84%) of ether **16**, bp 66–68° (3 mm), which showed 99% purity by glpc.

Material collected from glpc analysis exhibited the following physical properties: $n^{25}D$ 1.4446; ir (neat) 3.28, 6.10, 8.30, 8.90, 9.25, 9.39, 9.65, 10.18, 10.91, 11.43, 12.19 μ; nmr (CCl_4) τ 4.00–4.50 (m, 1, –CH=), 4.90–4.25 (m, 2, $=CH_2$), 5.51 (b s, 1, OCHO), 6.10–7.05 (m, 4, $-CH_2OCHOCH_2-$), 9.12 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.8; H, 11.0.

Tris-2-methyl-4-pentenyl Borate (17).—A mixture of 25 g (0.25 mol) of alcohol **14** and 5.25 g (0.084 mol) of boric acid in 250 ml of benzene was refluxed with constant removal of water. When the theoretical amount of water (4.5 ml, 0.25 mol) had separated, the solution was cooled slightly and the solvent was removed at reduced pressure to afford 27.2 g (100%) of colorless borate **17**: ir (neat) 3.30, 6.11, 6.78, 7.08, 7.51, 9.61, 10.06, 10.94 μ; nmr (CCl_4) τ 3.95–4.42 (m, 1, –CH=), 4.85–5.15 (m, 2, $=CH_2$), 6.35 (d, 2, J = 6 Hz, CH_2O), 7.65–8.50 [m, 3, $-CH_2CH(CH_3)-$], 9.08 (d, 3, J = 6 Hz, $CHCH_3$). This material was used without further purification.

2-Methyl-5-bromopentyl Acetate (6).—A solution of 12.84 g (0.09 mol) of acetate **15** and 0.22 g of benzoyl peroxide in 100 ml of hexane (98%) was cooled in an ice bath and anhydrous hydrogen bromide was rapidly passed through the solution for 15 min. The reaction was stirred for an additional 15 min, the excess gas was removed by a nitrogen sweep, and the total solution was washed well with a saturated aqueous solution of sodium bicarbonate and then brine until neutral. The hexane solution was dried ($MgSO_4$), concentrated under reduced pressure, and distilled to give 17.4 g (85%) of product, bp 69–72° (0.85 mm).

Further purification by distillation and glpc afforded material with the following physical properties: bp 69–71° (0.9 mm); $n^{33}D$ 1.4533 [lit.[16] bp 77° (3 mm); $n^{33}D$ 1.4539]; ir (neat) 5.73, 8.10, 9.63 μ; nmr (CCl_4) τ 6.14 (d, 2, J = 6.5 Hz, CH_2OAc), 6.63 (t, 2, J = 7 Hz, CH_2Br), 8.03 (s, 3, $COCH_3$), 9.06 (d, 3, J = 6.5 Hz, $CHCH_3$).

Anal. Calcd for $C_8H_{15}BrO_2$: C, 43.06; H, 6.78; Br, 35.82. Found: C, 43.0; H, 6.75; Br, 35.8.

2-Methyl-5-bromopentanol (8). A. From Tris-2-methyl-4-pentenyl Borate (17).—The procedure described for hydrobromination of acetate **13** was employed. From 0.24 mol of crude ester **17** there was obtained after 1 hr of reaction and aqueous work-up (washing with brine, saturated sodium bicarbonate solution, and brine) 41.5 g of crude product. Distillation afforded 36.8 g (86%) of clear bromo alcohol **8**, bp 70° (0.1 mm).

Redistillation afforded material with the following physical properties: bp 62° (0.02 mm); $n^{25}D$ 1.4829; ir (neat) 2.99, 9.68 μ; nmr (CCl_4) τ 4.30 (s, 1, OH), 6.61 (d, 2, J = 6 Hz, CH_2OH), 6.63 (t, 2, J = 6 Hz, CH_2Br), 9.07 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_6H_{13}BrO$: C, 39.79; H, 7.23; Br, 44.14. Found: C, 39.9; H, 7.2; Br, 44.1.

B. From 2-Methyl-5-bromopentyl Acetate (6).—The procedure of Nystrom[17] was employed. A mixture of 0.95 g (25 mmol) of lithium aluminum hydride and 25 ml of ether was treated in an anhydrous atmosphere with a solution of 3.33 g (25 mmol) of aluminum chloride in 38 ml of ether. A solution of 5.53 g (25 mmol) of bromo acetate **6** in 50 ml of ether was added dropwise over a 15-min period. The reaction mixture after stirring at room temperature for 1 hr was decomposed by the cautious addition of 9 ml of water followed by 35 ml of 6 N aqueous sulfuric acid in 25 ml of water. The resulting mixture was extracted with ether and the combined extracts were washed once with brine. Evaporation of the dried ($MgSO_4$) solvent and subsequent distillation afforded 4.18 g (94%) of bromo alcohol which was identical in all respects with the product **8** described above.

Tris-2-methyl-5-bromopentyl Borate (19).—The procedure described for preparation of borate ester **17** was employed on bromo alcohol **8**. From 18 g of crude bromo alcohol there was obtained 18.8 g (100%) of crude bromo borate **19**: ir (neat) 6.75, 7.05; 7.48, 9.68 μ; nmr (CCl_4) τ 6.38 (d, 2, J = 5.5 Hz, CH_2OB), 6.63 (t, 2, J = 6.5 Hz, CH_2Br), 9.10 (d, 3, J = 6 Hz, $CHCH_3$).

This material could be used directly without further purification.

2-Methyl-5-bromopentyl Tetrahydropyranyl Ether (7).—The procedure described for the preparation of ether **16** from the corresponding alcohol was employed. From 10.5 g (0.058 mol) of alcohol **8** there was obtained 15.4 g of crude product which was distilled to afford 15 g (96%) of colorless bromo ether **7**: bp 83–5° (0.02 mm); $n^{25}D$ 1.4729; ir (neat) 8.34, 8.91, 9.29, 9.41, 9.67, 10.21, 11.02, 11.46, 12.20 μ; nmr (CCl_4) τ 5.55 (s, 1, –OCHO), 6.10–7.05 (m, $-CH_2OCHOCH_2-$) 6.68 (t, J = 7 Hz, CH_2Br), 9.08 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{11}H_{21}BrO_2$: C, 49.82; H, 7.98; Br, 30.14. Found: C, 49.9; H, 8.1; Br, 30.1.

***endo*-3-Methyl-3-(4-methyl-5-hydroxypentyl)bicyclo[2.2.1]-heptan-2-one Tetrahydropyranyl Ether (10).**—A nitrogen-blanketed suspension of 4.9 g (0.125 mol) of a 61% mineral oil dispersion of sodium hydride in 60 ml of benzene was treated with a solution of 12.4 g (0.1 mol) of 3-methylnorcamphor in 60 ml of benzene. The resulting mixture was heated at 125° for 2 hr and then treated with a solution of 26.5 g (0.1 mol) of bromo ether **7** in 60 ml of benzene. The reaction was refluxed for an additional 61 hr, cooled, added to brine, and extracted with ether. The combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed to afford 33.5 g of oil. The crude product was distilled, bp 30–100° (0.02 mm), to remove starting materials, and the residual oil, 20.8 g (67%), composed mainly of product, was treated as described in the following experiment.

Pure keto ether **10** could be obtained by distillation: bp 135–140° (0.02 mm); ir (neat) 5.72, 8.31, 8.90, 9.28, 9.39, 9.67, 10.19, 11.00, 11.48, 12.19 μ; nmr (CCl_4) τ 5.53 (s, 1, OCHO), 6.11–7.10 (m, 4, $-CH_2OCHOCH_2$), 7.55, 7.68 (2 b s, 2, C_1 H, C_4 H), 9.02 (s, 3, CH_3), 9.06 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{19}H_{32}O_3$: C, 73.98; H, 10.46. Found: C, 73.9; H, 10.5.

***endo*-3-Methyl-3-(4-methyl-5-hydroxypentyl)bicyclo[2.2.1]heptan-2-one (11). A. From Keto Ether 10.**—A solution of 20.8 g (67 mmol) of crude keto ether **10** and 1.5 g of *p*-toluenesulfonic acid monohydrate in 250 ml of absolute ethanol was refluxed under nitrogen for 2 hr. The cooled reaction was added to brine and the product was isolated with ether. Removal of the dried ($MgSO_4$) solvent afforded 19.1 g of crude ketol **11** which on subsequent distillation afforded 14 g (96%) of product. Further purification by distillation and glpc gave ketol exhibiting the following physical characteristics: bp 127–130° (0.07 mm); ir (neat) 2.90, 5.73, 7.30, 9.60, 10.92, 13.02 μ; nmr (CCl_4) τ 6.72 (d, 2, J = 6 Hz, CH_2OH), 7.06 (s, 1, OH), 7.57, 7.71 (2 b s, 2, C_1 H, C_4 H), 9.07 (s, 3, CH_3), 9.16 (d, 3, J = 6.5 Hz, $CHCH_3$).

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 74.8; H, 10.8.

B. From Keto Borate 30.—A nitrogen-blanketed mixture of 4.9 g (0.125 mol) of a 61% mineral oil dispersion of sodium hydride and 60 ml of dry toluene was treated with a solution of 12.4 g (0.1 mol) of 3-methylnorcamphor in 60 ml of dry toluene and the resulting mixture was heated at 130° for 2.25 hr. The refluxing enolate solution was treated as rapidly as possible with a solution of 18.8 g (0.1 mol) of crude bromo borate **19** in 60 ml of dry toluene and subsequently refluxed for 68 hr. The cooled reaction was added to brine and the product was isolated with ether. Removal of the dried ($MgSO_4$) solvent and subsequent distillation afforded 13.9 g (62%) of ketol **11**, bp 117–130° (0.08 mm), which showed 90% purity by glpc. The material isolated by this process exhibited spectral properties identical with those of the ketol isolated from keto ether **10**.

***trans*-2,3-Dimethyl-*exo*-3-(4-methyl-5-hydroxypentyl)bicyclo-[2.2.1]heptan-2-ol (20). A. Using Methyllithium.**—A solution of 45 ml of 2.4 M ethereal methyllithium (0.11 mol) in 110 ml of ether was slowly treated (1 hr) with a solution of 8.0 g (35.7 mmol) of ketol **11** in 55 ml of ether. The reaction was stirred at room temperature for 3 hr and poured slowly onto crushed ice. The aqueous solution was saturated with salt and the product isolated with ether. Removal of the dried (Mg-

(16) S. V. Kessar and A. L. Rampal, *Chem. Ind. (London)*, 1957 (1963).
(17) R. F. Nystrom, *J. Amer. Chem. Soc.*, **77**, 2544 (1955).

SO_4) solvent and distillation afforded 8.2 g (96%) of product, bp 132° (0.18 mm). This material (95% purity by glpc) could be further purified by glpc: $n^{26.5}D$ 1.5019; ir (neat) 2.97, 7.31, 8.87, 9.69, 10.51, 10.60, 11.04 μ; nmr (CCl_4) τ 6.50–6.85 (m, 2, CH_2OH), 8.81 (s, 3, $HOCCH_3$), 9.11 (d, 3, J = 6 Hz, $CHCH_3$), 9.14 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{28}O_2$: C, 74.95; H, 11.74. Found: C, 75.0; H, 11.9.

B. Using Methylmagnesium Bromide.—A solution of 5.7 g (25 mmol) of ketol **11** in 50 ml of ether was added over 15 min to a nitrogen-blanketed solution of 33 ml of 3 *M* ethereal methylmagnesium bromide in 100 ml of ether. The mixture was refluxed for 5 hr and decomposed by the cautious dropwise addition of 20 ml of saturated aqueous sodium sulfate. The ethereal layer was decanted and the solid material was washed well with several portions of ether. The combined organic layers were washed once with the sodium sulfate solution and dried ($MgSO_4$), and the solvent removed. The crude oil (7.7 g) was distilled to give 5.58 g (93%) of 95% pure diol **20** possessing physical properties identical with those of material prepared in the proceeding experiment. The crude material could be used in subsequent reactions.

***trans*-2,3-Dimethyl-*exo*-3-(4-methyl-5-acetoxypentyl)bicyclo[2.2.1]heptan-2-ol (21).**—A nitrogen-blanketed solution of 2.6 g (11 mmol) of crude diol **20** in 13 ml of pyridine (distilled from barium oxide) was treated with 3.5 ml of acetic anhydride and the total was stirred at room temperature for 24 hr. The reaction was poured into brine and the product was isolated with ether. The combined extracts were washed with brine, 5% hydrochloric acid, and brine and dried ($MgSO_4$). Solvent removal and distillation afforded 2.8 g (89%) of hydroxy acetate **21**, bp 124–125° (0.05 mm). Material purified by glpc exhibited the following physical properties: ir (neat) 2.88, 5.72, 7.31, 8.05, 9.63 μ; nmr (CCl_4) τ 6.00–6.40 (m, 2, CH_2OAc), 8.04 (s, 3, $OCOCH_3$), 8.81 (s, 3, $HOCCH_3$), 9.08 (d, 3, J = 6 Hz, $CHCH_3$), 9.13 (s, 3, CH_3).

Anal. Calcd for $C_{17}H_{30}O_3$: C, 72.30; H, 10.71. Found: C, C, 73.6; H, 11.0.[18]

Dihydro-β-santalol Acetate (22).—The procedure described by Corey and coworkers[4] was employed. From 2.6 g of hydroxy acetate **21** (70% pure) there was obtained after distillation 2.06 g (77%) of product **22**, bp 120–125° (0.05 mm), which showed 85% purity by glpc. Redistillation and subsequent glpc purification afforded santalol acetate **22**: bp 90° (0.02 mm); $n^{32}D$ 1.4727; ir (film) 3.30, 5.72, 6.04, 7.32, 8.09, 9.65, 11.39 μ; nmr (CCl_4) τ 5.39, 5.64 (2 s, 2, $=CH_2$), 6.05–6.41 (m, 2, CH_2OAc), 7.41, 7.95 (2 b s, 2, C_1 H, C_4 H), 8.10 (s, 3, $OCOCH_3$), 8.99 (s, 3, CH_3), 9.09 (d, 3, J = 6 Hz, $CHCH_3$).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.0; H, 10.7.

This acetate was also prepared from dihydro-β-santalol in 82% distilled yield by routine procedures.

Dihydro-β-santalol (3). A. From Saponification of Acetate 22.—A mixture of 1.7 g (6.5 mmol) of acetate **22** (85% pure), 1.0 g (six pellets) of potassium hydroxide, and 15 ml of ethanol was stirred under nitrogen for 24 hr. The product was isolated with ether and distilled to afford 1.24 g (87%) of colorless dihydro-β-santalol, bp 93–103° (0.03 mm). The alcohol could be further purified by column chromatography (Florisil elution with 2–5% ether in hexane) or redistillation, bp 106–107° (0.1 mm), on larger scale. Material purified by glpc exhibited the following: $n^{26}D$ 1.4920; ir (neat) 3.00, 3.29, 6.03, 7.21, 9.01, 9.65, 11.37 μ; nmr (CCl_4) τ 5.31, 5.57 (s, 2, $=CH_2$), 5.87 (s, 1, OH), 6.65 (q, 2, J_1 = 6 Hz, J_2 = 4 Hz, CH_2OH), 7.35, 7.89 (2 s, 2, C_1 H, C_4 H), 8.96 (s, 3, CH_3), 9.09 (d, 3, J = 6 Hz, $CHCH_3$); mass spectrum parent ion *m/e* 222.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.9; H, 11.8.

B. From Wittig Reaction on Borate 30.—The preparation of borate **30** from ketol **11** *via* azeotropic removal of water was accomplished as previously outlined. From 9.4 g (42 mmol) of ketol and 0.88 g (14 mmol) of boric acid there was obtained 10.4 g of crude borate **30**: ir (film) 5.72, 7.08, 7.50, 9.69, 10.59, 10.98 μ. The crude borate was used directly as follows. A mixture of 4.9 g (125 mmol) of a 61% mineral oil dispersion of sodium hydride and 100 ml of anhydrous dimethyl sulfoxide was heated at 70° under nitrogen for 1 hr. The resulting solution was cooled to 0° and treated with a warm solution of 49 g (137 mmol) of methyltriphenylphosphonium bromide in 150 ml of anhydrous dimethyl sulfoxide. The resulting mass was allowed to warm to room temperature, was stirred for 0.5 hr, and was treated with a solution of 10.4 g (42 mmol) of borate **30** in a small amount of ether. The reaction was stirred for 0.5 hr at room temperature and 24 hr at 70°. The cooled reaction was added to water and the product was isolated with pentane. The organic solution was washed with water and brine and dried ($MgSO_4$) and the solvent was removed at reduced pressure. Subsequent distillation afforded 8.87 g (95%) of clear santalol product 3 (87% pure by glpc) identical with the product previously isolated.

C. From Boron Trifluoride Etherate Dehydration of Diol 20.—A solution of 5.58 g (23.3 mmol) diol **20** in 23 ml of ether was rapidly treated under nitrogen with 2.33 ml of a 47% boron trifluoride etherate solution. The dark reaction was refluxed for 2 hr, cooled, and cautiously added to an excess of saturated aqueous sodium bicarbonate solution. The product was isolated with ether, washed with brine, and dried ($MgSO_4$) and the solvent was removed at reduced pressure. The residual oil was distilled to afford 4.55 g (87%) of santalol **3** which showed 98% purity by glpc. This material exhibited spectral properties identical with those previously described.

The conversion of ketol **11** to santalol **3** could be carried out by removing most of the ether solvent from the crude, dried solution of diol **20** and treating this solution (0.03 mol of **20**/30 ml of ether) with boron trifluoride etherate as described above. This treatment afforded, on work-up and distillation, bp 111–118° (0.08 mm), a 75% yield of 96% pure dihydro-β-santalol (**3**).

D. From Wittig Reaction on Ketol 11.—Essentially the same procedure employed on keto borate **30** was used in an effort to convert ketol **11** to santalol **3**. From 0.91 g of ketol **11** there was obtained 2.55 g of crude Wittig product which was chromatographed on 100 ml of Florisil. Several early 5% ether in hexane fractions containing rearranged product **23** were combined (225 mg) and pure material was isolated by preparative glpc. The purified hydroxy olefin **23** exhibited the following spectral properties: ir (neat) 2.96, 3.28, 6.10, 9.42, 10.03, 10.96 μ; nmr (CCl_4) τ 4.45 (m, AA'BX, 1, J_{AB} = 17 Hz, $J_{A'B}$ = 10 Hz, J_{BX} = 7 Hz, $>CH_XCH_B{=}CH_AH_{A'}$), 5.18 (d, 1, J_{AB} = 17 Hz, $=CH_AH_{A'}$), 5.21 (d, 1, $J_{A'B}$ = 10 Hz, $=CH_AH_{A'}$), 6.50 (d, 1, J = 4 Hz, CHOH), 9.02 (d, 3, J = 7 Hz, $CHCH_3$), 9.21 (s, 3, CH_3).

Latter 5% ether in hexane and 10% ether in hexane fractions yielded 278 mg of santalol product **3** which was subsequently evaporatively distilled to give 210 mg of oil identical with santalol isolated from the experiments described above.

***endo*-3-Methyl-3-(4-methyl-5-hexenyl)bicyclo[2.2.1]heptan-2-one (25).**—An ice-cooled solution of 100 mg of hydroxy olefin **23** in 5 ml of acetone was treated dropwise with Jones reagent[19] until a persistent red color developed. The reaction was stirred for an additional 15 min and the product was isolated with ether. The ether was washed with saturated sodium bicarbonate and brine and dried ($MgSO_4$), and the solvent was removed at reduced pressure to afford 89 mg (90%) of keto olefin **25**. Evaporative distillation afforded a purified sample which exhibited the following spectral properties: ir (neat) 3.30, 5.73, 6.11, 10.03, 10.95 μ; nmr (CCl_4) τ 4.46 (m, AA'BX, 1, J_{AB} = 17 Hz, $J_{A'B}$ = 10 Hz, J_{BX} = 7 Hz, $>CH_XCH_B{=}CH_AH_{A'}$), 5.19 (d, 1, J_{AB} = 17 Hz, $=CH_AH_{A'}$), 5.22 (d, 1, $J_{A'B}$ = 10 Hz, $=CH_AH_{A'}$), 9.05 (d, 3, J = 7 Hz, $CHCH_3$), 9.09 (s, 3, CH_3).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.8; H, 11.1.

Tetrahydro-β-santalol (31).—A solution of 0.67 g (3 mmol) of dihydro-β-santalol (**3**) in 15 ml of ethanol was hydrogenated over 1 hr using 50 mg of prereduced platinum oxide in 10 ml of ethanol. The catalyst was removed by filtration and the solvent was removed at reduced pressure to afford 0.76 g of oily residue. Hickman distillation, bp 120–145° (0.1 mm), afforded 0.56 g (84%) of colorless product which showed >95% purity by glpc.

Material collected by preparative glpc exhibited the following physical properties: $n^{27}D$ 1.4866 (lit.[12] $n^{20}D$ 1.4918); ir (neat) 3.00, 7.22, 7.26, 9.60 μ; nmr ($CDCl_3$) τ 5.65 (s, 1, OH), 6.68 (m,

(18) Efforts to obtain a carbon analysis consistent with the assigned structure **21** were unsuccessful. The method of synthesis and the properties exhibited by the compound, however, leave no doubt as to the assigned structure.

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2, CH_2OH), 9.08, 9.12, 9.18, 9.25 ($CHCH_3$'s); mass spectrum parent ion m/e 224.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.3; H, 12.5.

Registry No.—**3,** 34289-89-9; **5,** 4154-60-3; **6,** 17142-58-4; **7,** 33454-43-2; **8,** 26496-79-7; **10,** 34288-62-5; **11,** 34288-63-6; **13,** 34289-91-3; **14,** 5673-98-3; **15,** 17142-57-3; **16,** 34288-66-9; **17,** 26496-78-6; **19,** 26496-80-0; **20,** 26133-24-4; **21,** 34289-93-5; **22,** 34288-69-2; **25,** 34288-70-5; **31,** 34288-71-6.

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Conformations of Acetylated Glyculose Phenylosotriazoles and Para-Substituted Phenylosotriazoles[1-3] in Solution

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Phenylosotriazoles and some para-substituted phenylosotriazoles of D-*erythro*- and L-*threo*-pentulose, D-*arabino*-, D-*lyxo*-, and L-*xylo*-hexulose, and 6-deoxy-L-*arabino*-hexulose have been examined as their peracetates by nmr spectroscopy at 100 MHz in chloroform-*d* solution. In each example, shielding of the protons along the side chain increases with distance from the heterocycle. From the spin–spin coupling data it can be inferred that the carbohydrate chain adopts a planar, zigzag arrangement of carbon atoms unless an eclipsed, 1,3 interaction between polar groups would thereby be generated or unless the polar substituent at C-2 (of the side chain) would thereby bisect the angle between the substituents on C-1, namely, the heterocycle and an acetoxyl group. Except for the arabino derivatives, which appear to be stabilized by stereochemical factors further along the chain, the favored conformations adopted when either or both of the aforementioned features would be present in the planar, zigzag arrangement are derived from the planar form by rotation about one or more of the carbon–carbon bonds along the chain. The variations of conformational preference displayed by the various acetylated, acyclic sugar derivatives examined to date are not presently amenable to more than superficial rationalization on the basis of apparent "size" of the chain-terminal group.

Conformational analysis of acyclic molecules can be traced back to van't Hoff[5] and to a casual observation by Rosanoff.[6] The statements of these authors were as general as they were fundamental, and the validity of their interpretations has not declined in the intervening years. Later interpretations of phenomena related to conformational properties of acyclic sugar molecules[7] drew specific conclusions that have been refuted.[8,9]

Recent work[2,9-20] has employed nmr spectroscopy to determine the conformational preferences of a variety of acyclic carbohydrate derivatives. In the initial paper of this series[10] the planar, zigzag arrangement of the carbon atoms in the side chain of 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline and its tetraacetate was inferred to be the favored conformation by consideration of vicinal, proton–proton spin couplings as they relate to approximate angular dependences.[21] Implicit, qualitative corrections for the effects of substituent electronegativity[22] were made by assuming couplings of 2–4 Hz for gauche, vicinal protons and 8–9 Hz for vicinal, antiparallel protons, by analogy with data for acetylated, cyclic, carbohydrate systems.[23-25] Similarly, for a series of nonacetylated phenylosotriazole derivatives, the planar, zigzag arrangement of the carbohydrate chain was shown[11] to be favored, except when this would lead to a parallel, 1,3 interaction between oxygen atoms on the chain; such an interaction, as arising in L-*xylo*-hexulose phenylosotriazole, is alleviated by the molecule's adopting a different rotameric form about one or more of the carbon–carbon bonds of the chain.

Examination of a configurationally complete series of acetylated diethyl dithioacetals confirmed[12] the influence of parallel, 1,3 interactions in determining favored conformations of acyclic molecules. Coupling data for members having the ribo and xylo configurations indicate that, by rotation about C-3–C-4 or C-2–C-3, respectively, stabilization is achieved by the generation of "sickle" conformers free of 1,3 interactions. The corresponding acetylated diphenyl dithioacetals[13,14] show essentially identical behavior, except for

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