= 1.26 where n is the index of refraction of water at 589 nm.

The calculation was applied to 13 cyclohexanepolyols for which experimental data are available and for which the predominant chair form (${}^1C_4$ or ${}^4C_1$) can be predicted from a presumed preference for equatorial hydroxyl groups. The results are shown in Table I and Figure 1. In Table I the calculated results are compared with the results of a purely empirical treatment of the same molecules[1] and with a previous semiempirical calculation.[5]

For all of the molecules, the calculation results in one CD rotational strength at particularly low energy, well separated from higher energy rotational strengths; it typically occurs near 155 nm. It is this rotational strength that determines the sign and, to a large extent, magnitude of the sodium D rotation. This result is similar to what was observed for the more complex saccharide structures, in which case it was shown to arise from the local geometry of tetrahedral carbon atoms in a puckered-ring structure.[8]

The present model sheds light on the fact that purely empirical treatments[1-3] are rather successful even though they are based on simple group additive contributions to optical activity. In terms of the present model, the sign and order of magnitude of the sodium D rotation are determined largely by a single vacuum UV CD band, whose position and intensity are determined largely by local symmetry. Group interactions do not qualitatively change that pattern. The effect of group interactions can be seen in Table I, in that the calculated values are not exact multiples of a constant rotation; they are, however, approximately multiples of 37°. The scatter in Figure 1 arises from the approximate nature of the semiempirical model itself and also from omitting the effects of small amounts of the less favored chair form, slight variations in chair geometry, and the potential for intramolecular hydrogen bonding in some of the compounds.

Although the optical activity of cyclohexanepolyols has been treated previously, the theory described here is the first to display the connection between molecular structure and sodium D rotation explicitly in terms of high energy vacuum UV CD features which are intrinsically related. It therefore represents a conceptual advance in spite of its necessarily approximate nature.

Acknowledgment. This work was partially supported by NSF Grant CHE85-09520.

Communications

Unrecognized Benzoyl Migrations in the Lincosamine Series: Modeling of the Electrophilic Reactions of an Alkenylpyranoside

Summary: Migration of a C_4 benzoyl group to C_6 is actuated by electrophilic attack on the double bond (C_6–C_7) of an alkenylpyranoside. Upon treatment of the resultant product with DBN, the benzoyl group migrates back to C_4 and a C_6–C_7 oxirane is produced.

Sir: Recently a fully synthetic route to racemic β-methyllincosaminide (**5**) was reported.[1] An important subgoal of that synthesis was the conversion of alkenylpyranoside **1** to epoxide **4**. A two-step sequence, passing through an intermediate bromohydrin, achieved the required transformation. In the first step, involving reaction of **1** with N-bromosuccinimide in aqueous acetic acid, a product $C_{30}H_{29}BrO_9$, mp 206–207 °C, corresponding to the overall addition of the elements of HOBr, was obtained in 92% yield (Figure 1). Treatment of this compound with 1,5-diazabicyclo[4.3.0]non-5-ene resulted in the loss of the elements of HBr and afforded the required epoxide **4**, mp 198–199 °C, in 96% yield.

These data per se did not distinguish between the two possible vicinal bromohydrins **2** and **3**. The compound was formulated as the former structure. The preference was based on the surmise[2] that a cyclic α-face bromonium specie derived from **1** would undergo solvolytic inversion at C_7. The configuration of the bromine atom in the bromohydrin is α (in the conformation drawn), since the derived epoxide had the configuration shown in **4**.

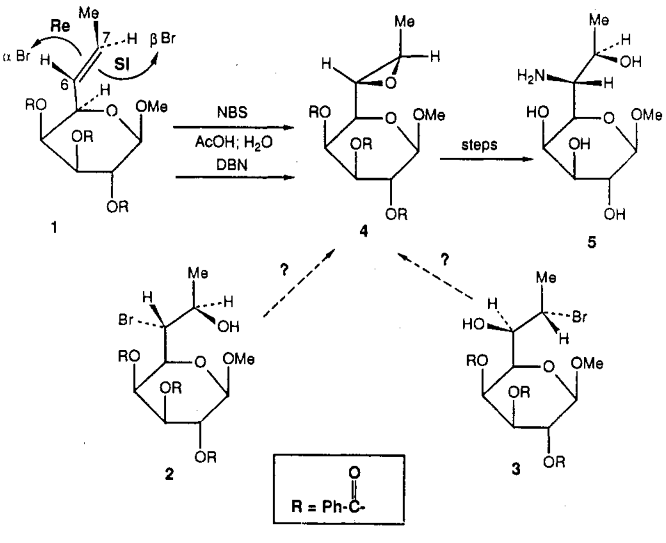

Figure 1.

By the recent arguments articulated by Chamberlin, Hehre, and co-workers,[3,4] the observed sense (α) of bromonium attack would be in accord only with that expected from a pathway where there is participation from an internal nucleophile. In the absence of such participation, these rules predict the preferred formation of the β-bro-

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[1] Danishefsky, S. J.; Larson, E.; Springer J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274.

[2] Our experiences in this area indicated that attack at C_7 is much less sterically encumbered than is attack at C_6. Contributing to the bias was an NMR measurement which seemed to indicate coupling between the C_7 and hydrolytic protons. This additional coupling, which is no longer seen, must have been due to some unexplained artifact.

[3] Kahn, S. D.; Pau, C. F.; Chamberlin, A. R.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 650.

[4] (a) Chamberlin, A. R.; Mulholland, R. L., Jr.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672. (b) We were prompted to reinvestigate this product by a private communication from Professor A. R. Chamberlin.

0022-3263/87/1952-3171$01.50/0

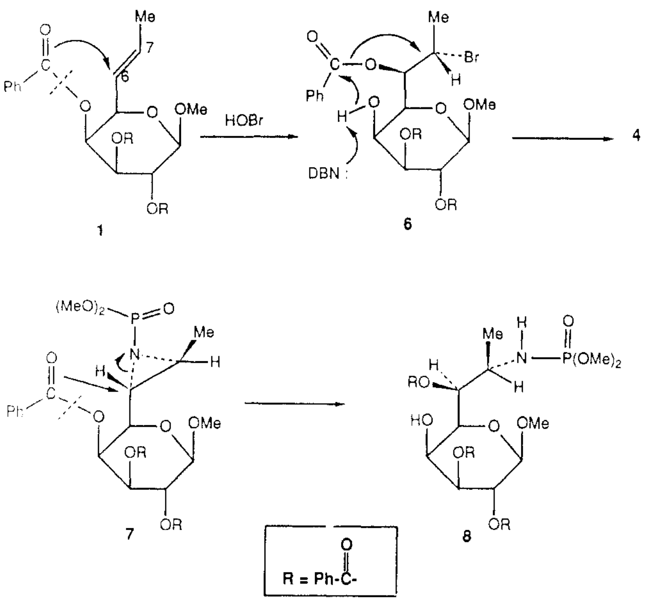

Figure 2.

monium specie via *si* face attack (i.e., bromonium forms syn to the pyranosidal oxygen.[3,4] The obvious possibility for a participating group would be the benzoyloxy function at position 4. With this in mind, the structure of the bromohydrin was investigated anew.

In fact, the bromohydrin was shown to be **6** (see ORTEP structure below) by a single-crystal X-ray determination.[5,6] *Thus, while the stereochemistry of the bromine had been correctly assigned, an unrecognized, $C_4 \rightarrow C_6$ benzoyl migration had occurred, leading to a 1,4-bromohydrin with the free hydroxyl group at the 4-position.* Upon treatment with DBN, a benzoyl migration in the opposite sense (from $C_6 \rightarrow C_4$) set the stage for formation of epoxide **4**. The benzoyl migration, which occurred in the formation of **6** from **1**, was missed because its effects were reversed in the second rearrangement leading from **6** → **4** (Figure 2). The $C_4 \rightarrow C_6$ benzoyl migration finds close analogy in the rearrangement of **7** → **8** observed during our previous work.[1]

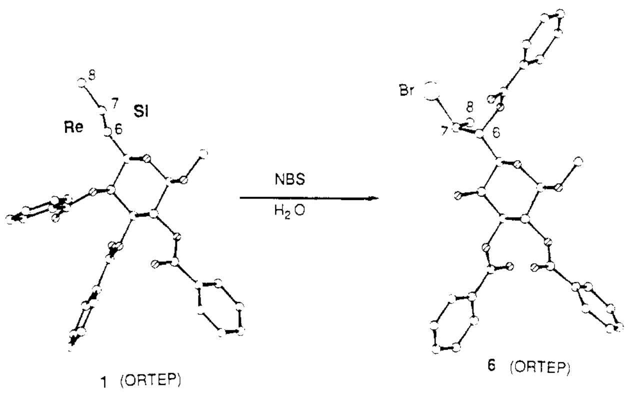

Figure 3.

Assuming that the conformation of structure **1** in Figure 1 is operative (vide infra), attack of the bromine-based electrophile has occurred from the *re* face and was accompanied by overall benzoyl migration. It will be recalled that the same *re* face suffers attack by osmium tetraoxide in a process which presumably does not involve benzoyl participation.[1] It was of interest to learn more about the most stable conformation of compound **1**. Fortunately, it could be obtained in crystalline form. An ORTEP drawing of compound **1** is shown in Figure 3.$_{6,7}$

It is interesting to note that the ground state of **1**, at least in the crystal,[8] corresponds to that used in the empirical correlations of Kishi and colleagues[9,10] to explain the sense of osmylation of double bonds bearing allylic hetero atoms. *It will further be noted that this ground-state conformation is not well predisposed for re face attack with near concerted participation by the C_4-benzoate.* Any such process, from a conformer resembling that shown in the ORTEP would only have been possible through *si* face attack. This would give the wrong stereochemistry for the bromine.

One interpretation which presents itself is that attack of the bromine-based electrophile occurs on a conformer similar to **1**, from the more hindered *re* face for stereoelectronic reasons similar to those advanced by Kishi.[6,9] By this view, rotation about the C_5–C_6 bond occurs after electrophilic attack but before benzoyl migration. Alternatively, attack of the electrophile occurs on a conformer

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(5) Summary of X-ray analysis: All data processing was done on a departmental Digital Equipment Corp. VAX 11/750 using the Enraf Nonius SDP-PLUS programs. The programs URANUS and SKK-PUB, plot and tables programs, respectively, were written by Simon Kay Kearsley, Yale University, 1985. The structure of GKS010, compound **6**, was determined by X-ray crystallography using a crystal which measured 0.20 × 0.18 × 0.10 mm. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated diffractometer using graphite monochromated Cu Kα radiation. Preliminary indications of the unit cell based on 25 randomly selected reflections revealed triclinic symmetry with the following lattice parameters: a = 6.528 (2) Å, b = 12.939 (3) Å, and c = 17.834 (4) Å, with α = 98.06 (2)°, β = 92.62 (2)°, and γ = 96.11 (2)°. The space group was assigned as $P\bar{1}$, with one molecule of composition $C_{30}H_{29}O_9Br$ forming the asymmetric unit. The calculated density was 1.376 g/cm^3. There were 3941 reflections collected with $2\theta \le 114°$; of those reflections, 2384 (60%) with 1 ≥3δ| were adjudged observed. The structure was solved by using MULTAN80. The phasing of 410 Es ≥ 1.569 resulted in an electron density map which revealed 35 of the 40 atoms which comprise the non-hydrogen structure. These 35 atoms were input into Normal using the WFO option, and the entire structure was apparent in the resulting electron density map. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were calculated by using SDP program HYDRO and added to the structure calculations. The following full-matrix refinement of the non-hydrogen atoms and addition of the hydrogen atoms to the structure factor calculations, without refinement of their positions, resulted in convergence to a standard crystallographic unweighted residual of 0.044 and a weighted residual of 0.058. All intramolecular bond distances and angles with the exception of the carbons comprising one of the benzoates are within normal ranges.

(6) Tables containing fractional coordinates, temperature factors, bond distances, torsional angles, and anisotropic temperature factors for compounds 1 and 6 are available as supplementary material.

(7) Summary of X-ray analysis: The structure of GKS020, compound 1, was determined by X-ray crystallography using a crystal which measured 0.27 × 0.25 × 0.17 mm. Diffraction measurements were made on an Enraf-Nonius CAD-4 fully automated diffractometer using graphite monochromated Cu Kα radiation. Preliminary indications of the unit cell, based on 25 randomly selected reflections, revealed orthorhombic symmetry with the following lattice parameters: a = 10.452 (3) Å, b = 20.025 (5) Å, and c = 26.736 (4) Å, with $\alpha = \beta = \gamma$ = 90.0°. The space group, based on the observed systematic extinctions, could be assigned as *Pbca*, Z = 8, with one molecule of composition $C_{30}H_{28}O_8$ forming the asymmetric unit. The calculated density was 1.226 g/cm^3. There were 3603 reflections collected with $2\theta \le 114°$; of those reflections, 2013 (56%) with 1 ≥ 3 δ| were adjudged observed. The structure was solved by using MULTAN80. The phasing of 352 Es ≥ 1.714 resulted in an electron density map which revealed the entire non-hydrogen structure. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were calculated by using SDP program HYDRO and added to the structure calculations. The following full-matrix refinement of the non-hydrogen atoms and addition of the hydrogen atoms to the structure factor calculations, without refinement of their positions, resulted in convergence to a standard crystallographic unweighted residual of 0.048 and a weighted residual of 0.044. All intramolecular bond distances and angles with the exception of the carbons comprising the olefin are within normal ranges.

(8) The reactive conformer may not necessarily reflect the conformation in the crystalline ground state. See: Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111.

(9) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943.

(10) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947.

drastically different from that of the ground state, with near concerted participation by the benzoyl group in the Chamberlin-Hehre sense. Our data do not provide the means to distinguish between these views.

Acknowledgment. This work was supported by PHS Grant AI 16943. Crystallographic measurements and computations were carried out on facilities supported by the Yale Chemical Instrumentation Center. We thank Professor A. R. Chamberlin of the University of California at Irvine for a stimulating communication (see ref 4).

Supplementary Material Available: ORTEP drawings of compounds 1 and 6 and tables containing fractional coordinates, temperature factors, bond distances, torsional angles, and anisotropic temperature factors for 1 and 6 (15 pages). Ordering information is given on any current masthead page.

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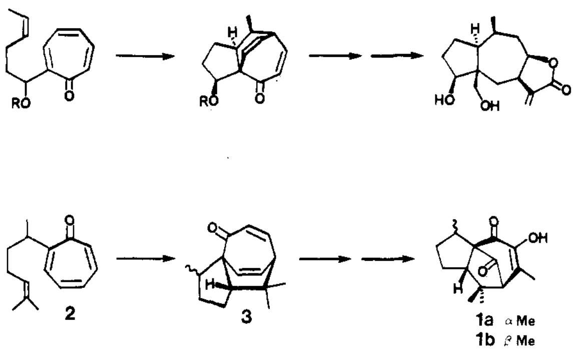
A New Approach to the Cedrane Ring System via Intramolecular [4 + 2] Tropone-Olefin Cycloaddition. Total Synthesis of (±)-α- and (±)-β-Pipitzol

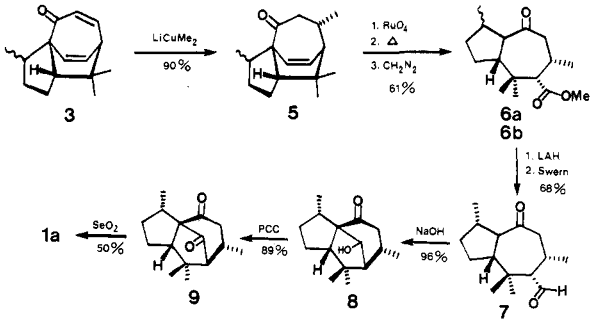
Summary: A new strategy for the preparation of polycarbocyclic natural products is demonstrated by a concise transformation of an intramolecular tropone-olefin cycloadduct (**3**) to the cedrane ring system of the pipitzols (**1a,b**).

Sir: We have recently demonstrated that intramolecular [6 + 4] and [4 + 2] tropone-olefin cycloadditions proceed smoothly and with high stereoselectivity.[1] The [4 + 2] cycloaddition reactions typically afford endo cycloadducts that possess both bicyclo[5.3.0]decane and bicyclo[3.2.2]nonane substructures as depicted in Scheme I. Thus, these cycloadducts can be conceivably transformed into various naturally occurring ring systems. For example, removal of the olefinic two-carbon bridge would leave the perhydroazulene ring system of the pseudoguaianolides (Scheme I). Alternatively, excision of one carbon of the olefinic two-carbon bridge would provide the bicyclo[3.2.1]octane subunit of the cedrane class of compounds (Scheme I). Herein, we verify that the latter ring transmutation is indeed viable and report on the total syntheses of β- and α-pipitzol (**1a,b**),[2] two highly oxygenated members of the cedrane family.

Scheme I



Scheme II



It was recognized that the 5:1 (αMe:βMe) diastereomeric mixture of enones **3**, obtained from the thermal (240 °C, 72 h; 85%) or catalyzed (0.1 equiv of Et_2AlCl, 110 °C, 36 h; 88%) [4 + 2] cycloaddition reaction of tropone **2**,[3] contained sufficient functionality for further elaboration into pipitzol. As alluded to previously, the major operation dictated by this synthetic strategy is the transformation of the bicyclo[3.2.2]nonane substructure present in **3** to the bicyclo[3.2.1]octane subunit present in the pipitzols (**1a,b**). In addition, a fourth methyl substituent must be introduced. To this end, conjugate addition of lithium dimethylcuprate to the enones **3** proceeded with high stereoselectivity (>20:1) to afford ketones **5** in 90% yield. (Scheme II). The stereochemical assignment shown in **5** is tentative but is the expected consequence of addition from the less hindered α-face. Oxidative cleavage of the double bond of **5** according to the Sharpless methodology[4] ($RuCl_3$, H_2O, CH_3CN, CCl_4, HIO_4) and subsequent decarboxylation effected removal of the extraneous bridging carbon. Esterification (CH_2N_2) of the resulting mixture of keto acids furnished two keto esters **6** in 61% overall yield from **5**. The mixture of keto esters **6** could be separated by chromatography on silica gel. The synthesis was first completed with the major diastereomer **6a** (αMe, mp 89-90 °C). Subjection of **6a** to a reduction (LAH)-reoxidation (Swern[5]) sequence provided a single keto aldehyde (**7**) in 68% overall yield.

The crucial reconstruction of the bridged bicyclic system was smoothly realized upon treatment of **7** with 2% aqueous NaOH in refluxing MeOH, affording a single stereoisomer of the aldol product **8** (mp 138-140 °C) in 96% yield.[6] Oxidation of **8** (PCC) gave the crystalline

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(1) Funk, R. L.; Bolton, G. L. *J. Am. Chem. Soc.* **1986**, *108*, 4655.

(2) For isolation and structural elucidation, see: (a) Walls, F.; Padilla, J.; Joseph-Nathan, P.; Giral, F.; Romo, J. *Tetrahedron Lett.* **1965**, 1577. (b) Walls, F.; Padilla, J.; Joseph-Nathan, P.; Giral, F.; Escobar, M.; Romo, J. *Tetrahedron* **1966**, *22*, 2387. (c) Joseph-Nathan, P.; Roman, L. U.; Hernandez, J. D.; Taira, Z.; Watson, W. H. *Ibid.* **1980**, *36*, 731. (d) For an intriguing mechanistic study of the formation of α- and β-pipitzol, see: (e) Joseph-Nathan, P.; Mendoza, V.; Garcia, E. *Ibid.* **1977**, *33*, 1573. (f) Joseph-Nathan, P.; Sanchez, I. H.; Yanez, R.; Enriquez, R. *J. Org. Chem.* **1981**, *46*, 2818. For a formal total synthesis of β-pipitzol, see: (g) Sanchez, I. H.; Larraza, M. I.; Basurto, F.; Yanez, R.; Avila, S.; Tovar, R.; Joseph-Nathan, P. *Tetrahedron* **1985**, *41*, 2355.

(3) A modest increase in the relative asymmetric induction (6:1) was observed in the catalyzed reaction.

(4) Sharpless, K. B.; Chong, J. M. *J. Org. Chem.* **1985**, *50*, 1560 and ref 4 therein.

(5) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(6) Although construction of the bicyclo[3.2.1]octane ring systems via intramolecular aldol reactions of substituted cyclohexanones[7a-c] and cyclopentanones[7d-f] is a frequently employed strategy in natural product synthesis; the analogous closure of a substituted cycloheptanone appears to be quite rare.[8]

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