Studies in the Synthesis of Coriolin. An Approach to a Functionalized BC Ring System

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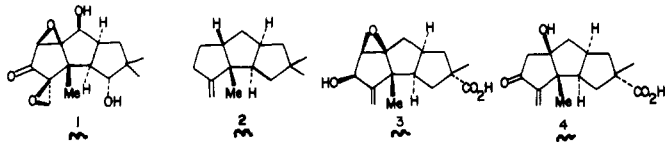
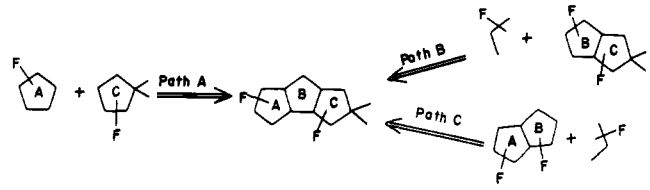
The conversion of methanoindene **8** into a highly functionalized intermediate that could be of use in a synthesis of coriolin (**1**) is described. The cyclopentenone **8** has been converted into the C ring of coriolin (**1**) with regiochemical and stereochemical control. Ozonolysis of the norbornenyl olefin and reductive workup gave **23**, in which five of the eight asymmetric centers are in the correct relative stereochemistry for eventual construction of coriolin (**1**). The differentiation of the primary hydroxymethyl groups in **23** was achieved by selective acylation with trimethylacetyl chloride (pivaloyl chloride). The structure of the major product of this reaction was proven to be **25** by X-ray crystallography. Studies of this acylation reaction were carried out on substrates having other functional groups attached to the C-1 hydroxy. A possible explanation of this somewhat surprising reactivity difference between the C-3 and C-8 hydroxymethyl groups is presented.

Coriolin (**1**) is a member of the *cis,anti,cis*-tricyclo[6.3.0.$0^{2,6}$]undecanoid (hirsutane) class of sesquiterpenes. It was isolated from the broth of the Basidiomycete *Coriolus consors*,[1] together with other structurally related compounds. The initial structural assignment was incorrect[2] and was later revised[3] to that shown in **1**.

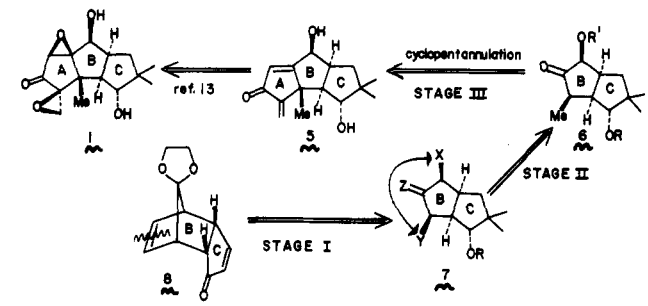


The biological activity[4] and the interesting and highly functionalized compact structure of coriolin (**1**) has led to a number of synthetic investigations into the hirsutane class of compounds.[5] Hirsutene (**2**) has been synthesized by several groups.[6] A number of other reports have appeared that have dealt with some very interesting and useful methods of forming the tricyclopentanoid ring system, as well as the chemistry associated with transformations in these series.[7] The first synthesis of hirsutic acid C (**3**) was reported by Matsumoto.[8] Lansbury and co-workers introduced the chloro olefin annulation se-

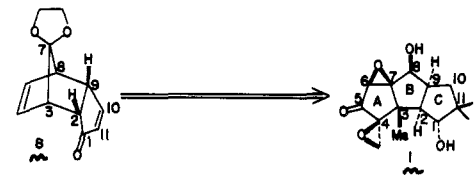
Scheme I



Scheme II



Scheme III



(1) (a) Takeuchi, T.; Iinuma, H.; Iwanaga, J.; Takahashi, S.; Takita, T.; Umezawa, H. *J. Antibiot.* **1969**, *22*, 215. (b) Takeuchi, T.; Iinuma, H.; Takahashi, S.; and Umezawa, H. *Ibid.* **1971**, *24*, 631.

(2) (a) Takahashi, S.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1969**, 4663. (b) Takahashi, S.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Ibid.* **1970**, 1637. (c) Kunimoto, T.; Umezawa, H. *Biochim. Biophys. Acta* **1973**, *318*, 78. (d) Nishimura, Y.; Koyama, Y.; Umezawa, S.; Takeuchi, T.; Ishizawa, M.; Umezawa, H. *J. Antibiot.* **1977**, *30*, 59.

(3) Takahashi, S.; Naganawa, H.; Iinuma, H.; Takita, T.; Maeda, K.; Umezawa, H. *Tetrahedron Lett.* **1971**, 1955.

(4) (a)e Ayanoglu, E.; Gebreyesus, T.; Beechan, C. N.; Djerassi, C.; Kaisin, M. *Tetrahedron Lett.* **1978**, 1671. (b) Takeuchi, T.; Takahashi, S.; Iinuma, H.; Umezawa, H. *J. Antibiot.* **1971**, *24*, 631. (c) Nakamura, N.; Takita, T.; Umezawa, H.; Kunishima, M.; Nakayama, Y.; Iitaka, Y. I. *J. Antibiot.* **1974**, *27*, 301. (d) Ishizuma, M.; Iinuma, H.; Takeuchi, T.; Umezawa, H. *Ibid.* **1972**, *25*, 230. (e) Kunimoto, T.; Umezawa, H. *Biochim. Biophys. Acta* **1973**, *318*, 78. (f) Ishizaka, M.; Iinuma, H.; Takeuchi, T.; Umezawa, H. *J. Antibiot.* **1972**, *25*, 320.

(5) For an excellent discussion of recent approaches to cyclopentanoid natural products, see *Tetrahedron* **1981**, *37*.

(6) (a) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1981**, *103*, 2744. (b) Greene, A. E. *Tetrahedron Lett.* **1980**, 3059. (c) Hudlicky, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T.; *J. Am. Chem. Soc.* **1980**, *102*, 6351. (d) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *Ibid.* **1979**, *101*, 6116. (e) Hayano, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1978**, 1991. (f) Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Ibid.* **1976**, 2795. (g) Nozoe, S.; Furukawa, J.; Sankawa, U.; Shibata, S. *Ibid.* **1976**, 195.

(7) (a) Shirahama, H.; Osawa, E.; Matsumoto, T. *Tetrahedron Lett.* **1978**, 1987. (b) See also Feline, T. C.; Mellows, G.; Jones, R. B.; Phillips, L. *J. Chem. Soc., Chem. Commun.* **1974**, 63. (c) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kagawa, S.; Sakan, F.; Matsumoto, S.; Nishida, S. *J. Am. Chem. Soc.* **1968**, *90*, 3280. (d) Matsumoto, T. *Tetrahedron Lett.* **1970**, 1171. (e) Ichihara, A.; Morita, J.; Kobayashi, K.; Kagawa, S.; Shirahama, H.; Matsumoto, T. *Tetrahedron* **1970**, *26*, 1331. (f) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kagawa, S.; Sakan, F.; Miyano, K. *Tetrahedron Lett.* **1971**, 2049. (g) Matsumoto, T.; Miyano, K.; Kagawa, S.; Yu, S.; Ogawa, J.; Ichihara, A. *Ibid.* **1971**, 3521. (h) Miyano, K.; Ohfune, Y.; Azuma, S.; Matsumoto, T. *Ibid.* **1974**, 1545. (i) Kagawa, S.; Matsumoto, S.; Shuji, N.; Yu, S.; Morita, J.; Ichihara, A.; Shirahama, H.; Matsumoto, T. *Ibid.* **1969**, 3913. (j) For model studies related to coriolin (**1**), see Hashimoto, H.; Ito, T.; Shirahama, H.; Matsumoto, T. *Heterocycles* **1979**, *13*, 151. (k) Little, R. D.; Bukhari, A.; Venegas, M. G. *Tetrahedron Lett.* **1979**, 305. (l) Little, R. D.; Muller, G. W. *J. Am. Chem. Soc.* **1979**, *101*, 7129. (m) Demuth, M.; Chandrasekhar, S.; Nakano, K.; Raghaven, P. R.; Schaffner, K. *Helv. Chim. Acta.* **1980**, *63*, 2440. (n) Hashimoto, H.; Ito, K.; Shirahama, H.; Matsumoto, T. *Heterocycles* **1979**, *13*, 159. (o) Knapp, S.; Trope, A. F.; Ornaf, R. M. *Tetrahedron Lett.* **1980**, 4301. (p) Knapp, S.; O'Connor, V.; Mobilio, D. *Ibid.* **1980**, 4557.

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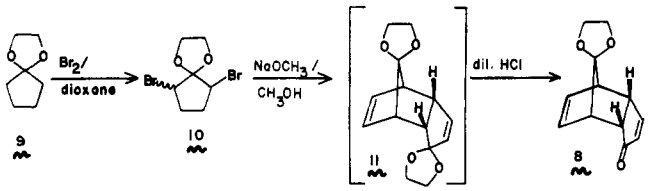
Scheme IV



quence in a route to norhirsutanes,[9] and later modified this methodology to synthesize hirsutic acids C (3)[10] and N (4).[11] Finally, Trost and co-workers synthesized hirsutic acid C (3) in a beautifully stereocontrolled fashion.[12] Three basic routes have been used to synthesize coriolin (1). The first couples A and C ring residues to form the system (Scheme I, path A). Another methodology utilizes the annulation of the A ring onto a functionalized BC system (Scheme I, path B). Finally, the C ring may be added to an intact AB nucleus (Scheme I, path C).

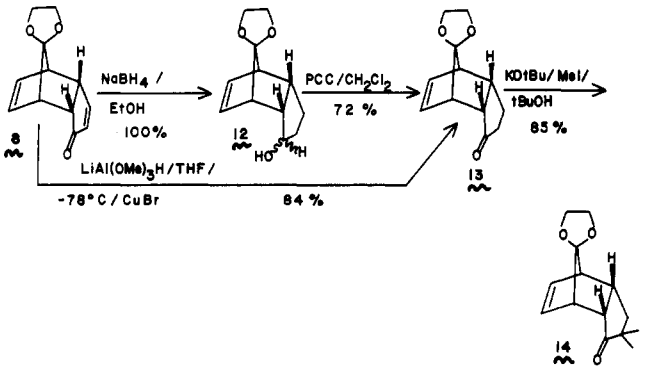
The first total synthesis of coriolin (1) was reported by Tatsuta[13] and followed the outline of path A. The Danishefsky route[14] used a unique method of A-ring annulation onto a preformed BC system (path B). These workers also developed methods for the stereoselective introduction of the A-ring epoxides. Overall, this led to an elegant synthesis of coriolin (1) which is fairly efficient and fully stereoselective. The third report of a coriolin (1) synthesis was by Ikegami.[15] This synthesis also annulates the A ring onto a BC system (path B) and uses some methodologies similar to the Danishefsky route to reach the target (1). Most recently, Trost[16] completed a versatile approach along the lines of path C.

We report here the results of our studies that have led to a relatively efficient synthesis of a functionalized coriolin BC ring system from readily available methanoindene 8.

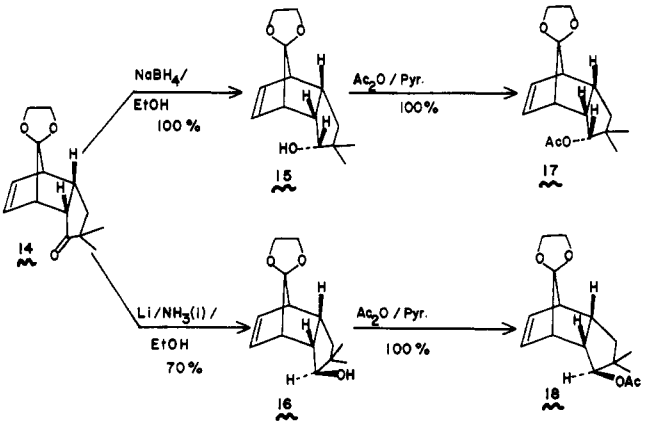
Synthetic Analysis. Our ultimate synthetic plan calls for the construction of the Danishefsky dienone 5. This compound has been converted to coriolin (1).[14] The last section of our route (Scheme II, stage III) would involve the annulation of the A ring onto a ketone such as 6. The penultimate goal (Scheme II, stage II) is to convert a functionalized and differentiated ($x \neq y$) bicyclo[3.3.0]-octane 7 into the central ketone 6. Thus, the immediate goal was to develop an efficient and stereoselective route to biscyclopentanoid 7.

The known methanoindene 8 was chosen as the starting material. There were several advantages to be gained by using this compound. Foremost, it can be shown (see numbering in Scheme III) that 8 contains a considerable amount of diverse and versatile functionality that will be useful for the eventual construction of the BC-ring system

Scheme V



Scheme VI



of coriolin (1). Oxidative cleavage of the norbornenyl olefin would afford the bicyclo[3.3.0]octane necessary for the B and C rings of coriolin (1). Furthermore, inherent rigidity of the bridged system provides a foundation for the introduction of key chiral centers because it undergoes highly stereoselective reactions. Finally, 8 is readily available in large quantities by modification of the procedures of Chapman[17] and Paquette.[18]

We now describe our route to a differentiated bicyclo-[3.3.0]octane such as 7.

Results and Discussion

Elaboration of the C-Ring Functionality. Enone 8 is prepared as shown in Scheme IV. Bromination[19] of cyclopentanone ethylene ketal 9[17] gave the dibromoketal 10. Dehydrobromination[17] of 10 occurred smoothly upon treatment with sodium methoxide to afford the dimer 11. Treatment of the dehydrobromination reaction mixture with dilute hydrochloric acid gave the enone 8. This two-step process produced 8 in 60–70% overall yield from ketal 9.

The first series of transformations involved generation the C-ring functionality. Initial attempts to introduce the C-11 geminal dimethyl groups by reductive alkylation[20] failed. Therefore, we decided to eliminate the α,β-unsaturation and then use more standard ketone alkylation procedures.

Two methods were developed to remove the conjugated olefin. Reduction of 8 with excess sodium borohydride (Scheme V) gave a nearly quantitative yield of alcohol 12,

(8) (a) Sakan, F.; Hashimoto, H.; Ichihara, A.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1971**, 3703. (b) Hashimoto, H.; Tzuzuki, K.; Sakan, F.; Shirahama, H.; Matsumoto, T. *Ibid.* **1974**, 3745.

(9) Lansbury, P. T.; Nazarenko, N. *Tetrahedron Lett.* **1971**, 1833.

(10) (a) Lansbury, P. T.; Nienhouse, E. J.; Scharf, D. J.; Hilfikir, F. R. *J. Am. Chem. Soc.* **1970**, *92*, 5649. (b) Lansbury, P. T.; Briggs, P. C.; Demmin, T. R.; DuBois, G. E. *Ibid.* **1971**, *93*, 1311. (c) Lansbury, P. T.; *Acc. Chem. Res.* **1972**, *5*, 311. (d) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1971**, 1829.

(11) Lansbury, P. T.; Wang, N. Y.; Rhodes, J. E. *Tetrahedron Lett.* **1972**, 2053.

(12) Trost, B. M.; Shuey, C. D.; DiNinno, F.; McElvain, S. S. *J. Am. Chem. Soc.* **1979**, *101*, 1284.

(13) Tatsuta, K.; Akimoto, K.; Kinoshita, M. *J. Antibiot.* **1980**, *33*, 100.

(14) (a) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *J. Am. Chem. Soc.* **1981**, *103*, 3460. (b) Danishefsky, S.; Zamboni, R.; Kahn, M.; Etheredge, S. J. *Ibid.* **1980**, *102*, 2097. (c) Danishefsky, S.; Zamboni, R. *Tetrahedron Lett.* **1980**, 3439.

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(16) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380.

(17) Chapman, N. B.; Key, J. M.; Toxne, K. J. *J. Org. Chem.* **1970**, *35*, 3860.

(18) Paquette, L. A.; James, P. R.; Klein, G. *J. Org. Chem.* **1978**, *43*, 1287.

(19) Eaton, P. A.; Hudson, R. A. *J. Am. Chem. Soc.* **1965**, *87*, 2769.

(20) Stork, G.; Nelson, G. L.; Rouessac, F.; Gringore, O. *J. Am. Chem. Soc.* **1971**, *93*, 3091.

Table I

compd acylated	% yield[a] major monopivalate	minor monopivalate	dipivalate	starting material	ratio of mono-/ dipivalate
23	63	1	15	21	4.2 1
19	27-34[b]	4-10[b]	40	10	0.9 1
30	48	3	22	27	2.2 1

[a] Isolated yields of products after a single reaction. [b] The monoesters were not completely separable. This number takes into account the portion of the ester also present in the mixed fractions (based on NMR analysis).

which was readily oxidized to the desired ketone **13** (72%) with pyridinium chlorochromate.[21] Alternatively, **13** can be prepared directly (see Scheme V) (84%) by 1,4-reduction of enone **8** with lithium trimethoxyaluminium hydride[22] in the presence of cuprous bromide.[23] The alkylation of **13** occurred smoothly upon treatment with methyl iodide and potassium *tert*-butoxide, to give dimethyl ketone **14** in 85% yield.

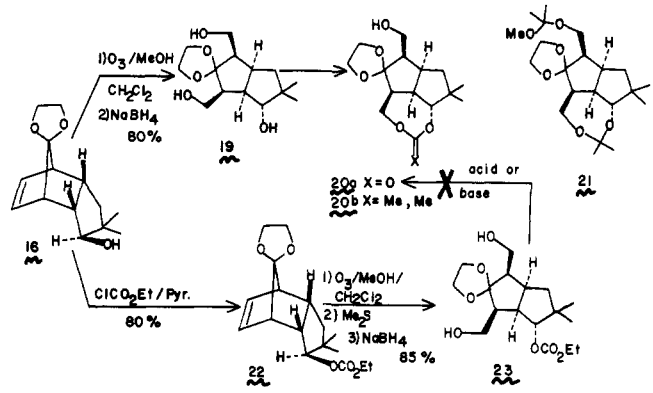
The functionality of the C ring would be complete upon reduction of the C-1 ketone to the exo alcohol. This would necessarily correspond to the endo attack of a hydride. Clearly, this is not the expected mode of attack for a nucleophile in a bridged system of this type (**14**). We were also unable to predict the effects (if any) of the large C-7 dioxolane on the steric course of the reaction.

Reduction of ketone **14** with sodium borohydride (Scheme VI) occurs via exo attack of hydride to give exclusively the endo alcohol **15** (100%). However, reduction with lithium in ammonia under thermodynamic conditions yielded only an isomeric alcohol **16** (70%) that exhibited physical and spectroscopic properties that were distinctly different than those of alcohol **15**. These complementary methods are highly stereoselective in this system. None of the diastereomeric alcohol was indicated by the analysis or isolated from either reduction procedure.

The initial assignment of the C-1 relative stereochemistry of the isomeric alcohols **15** and **16** was based on the proton nuclear magnetic resonance spectra (100 MHz) of the derived (acetic anhydride/pyridine) acetates **17** and **18** (100%). The C-1 proton of acetate **17** occurs as a doublet (J = 6.6 Hz) at δ 4.73, while the corresponding C-1 proton in **18** is displayed as a doublet (J = 7.4 Hz) at δ 4.16 or 0.57-ppm farther upfield. This chemical-shift difference is presumably the result of the more effective shielding of the C-1 proton of isomer **18** by the norbornenyl–olefinic bond. It must be recognized that this reasoning did not constitute undeniable evidence for the postulated structures. However, X-ray analysis of a later product verified beyond doubt the structural conclusions of the spectroscopic analysis (vide infra). Thus, with relative stereochemistry and functionality of the C ring completed, our attention turned to the liberation and elaboration of the B ring.

Formation of the B Ring. Ozonolytic cleavage of the norbornenyl[24] olefin **16**, followed by reductive workup with sodium borohydride (Scheme VII), produced triol **19** (80%). There were several plausible methods examined by which the C-3 and C-8 hydroxymethyls could be differentiated. Examination of molecular models showed that the formation of a seven-membered ring, such as **20**, containing the C-1 α-alcohol and the C-3 hydroxymethyl was very feasible. All attempts to prepare carbonate **20a** by

Scheme VII



standard methods (e.g., phosgene or *N,N'*-carbonyldiimidazole) led to mixtures of products that decomposed upon attempted purification. Treatment of **19** with 2,2-dimethoxypropane and pyridinium tosylate[25] rapidly formed a product identified as diacetonide **21** on the basis of spectroscopic data. Unfortunately, this compound was very unstable and reverted to triol **19** under the mildest of handling or reaction conditions.

An alternative method of preparing the carbonate **20a** was examined. We reasoned that the intramolecular formation of **20a** would be much easier to achieve. Thus, reaction of alcohol **16** with ethyl chloroformate in pyridine gave the carbonate **22** (80%) (Scheme VII). Ozonolysis of **22**, followed by direct treatment with dimethyl sulfide and sodium borohydride, afforded the desired diol **23** in 85% yield. However, all our attempts to effect intramolecular transesterification using acidic, basic, or neutral conditions resulted in either decomposition or recovery of diol **23**. Consequently, the approach to internal differentiation by an intermediate such as **20** was abandoned.

The examination of models of **19** and **23** offered little possibility that one of the primary alcohols would react regiospecifically (e.g., acylation). The only environmental difference is the relatively remote C-1 α-oxygen. However, it did seem possible that an intramolecular hydrogen bond could form between the C-1 α-oxygen and the proximal C-3 hydroxymethyl. It was on this basis that we attempted the acylation reaction described below. The trimethylacetyl (pivaloyl) group was chosen because its high steric demand might amplify any regioselectivity difference. Treatment of **23** (Scheme VIII) with pivaloyl chloride in pyridine at −15 °C gave four compounds, **23–26**, which were easily separated. The major product (63%) was a monopivalate ester. The dipivalate ester (15%) and the regioisomeric monopivalate (1%) were also identified, and the starting diol **23** (21%) was recovered.[26] The isolated yields after recycling the recovered diol **23** once were as follows: major monopivalate, 75%; minor monopivalate,

(21) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(22) Eliel, E. L.; Sanda, Y. *Tetrahedron Lett.* **1970**, 2411.
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(24) Frickel, F. *Synthesis* **1974**, 507.
(25) Miyashita, M.; Yoshikoshi, A.; Grieco, P. A. *J. Org. Chem.* **1977**, *42*, 3732.
(26) These numbers represent isolated yields of pure products.

Scheme VIII

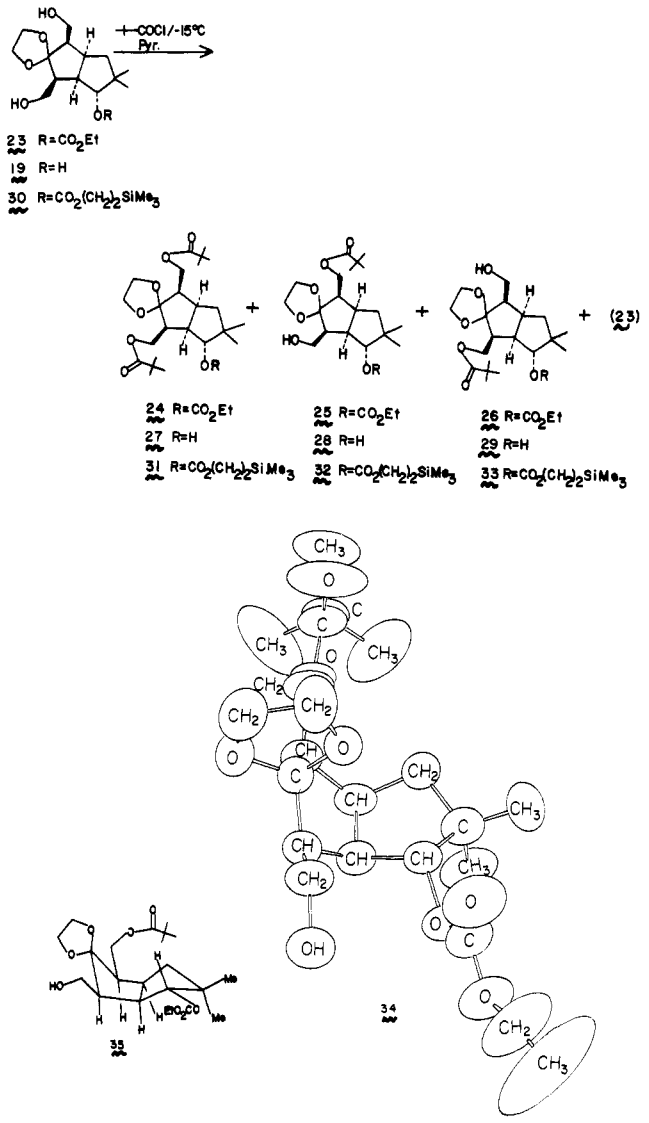


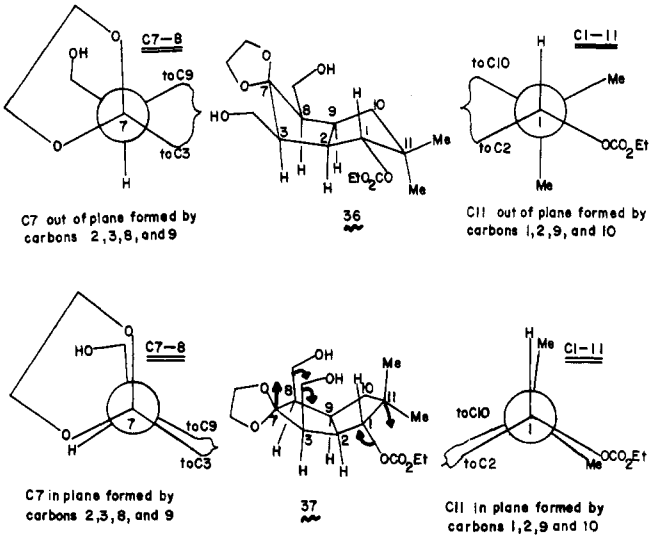
Figure 1. ORTEP drawing of compound **25** with 50% ellipses. No hydrogen atoms are shown.

2%; dipivalate, 21%; diol **23**, 1%. Thus, considerable regioselectivity is exhibited in this reaction.

A series of experiments were done to determine if the nature of the C-1 substituent affected the regioselectivity. Compounds **19** and **30**[27] were acylated under the conditions described for **23**. The results are shown in Table I. The yields indicate (viz. **23** and **30** vs. **19**) that the regioselectivity is enhanced if the C-1 α-oxygen is attached to a large group.

Although a high degree of selectivity is evidenced in the acylation reaction, there was no firm basis on which to judge whether the major monopivalate was **25** or **26**. Spectroscopic evidence could not furnish the necessary information. The regiochemistry of the pivaloylation of **23** was determined by X-ray analysis. The results (see **34** and **35**) indicate that the C-8 hydroxymethyl is preferentially acylated. Therefore, monopivalate **25** is the major product. The X-ray structure also positively confirms the fact that the thermodynamic reduction of the C-1 ketone gave the exo alcohol (see Scheme VI, **14** → **16**).

Examination of this structure (**34**) also leads to a possible explanation for the great reactivity difference in the acylation of the primary alcohols. The C-7 carbon is above the plane formed by the other four carbon atoms of the B ring, and the C-11 carbon is below the plane formed by the four carbons of the C ring. A least-squares planes[28] analysis shows that C-7 is 0.66 Å above the plane formed by C-2, C-3, C-8, and C-9, and C-11 is 0.70 Å below the plane formed by C-1, C-2, C-9, and C-10. This distortion relieves the eclipsing interactions (see **36** and **37**) involving C-3, C-7, and C-8, as well as C-1, C-10, and C-11.



It thereby allows the C-3 and C-8 hydroxymethyl groups to exist in a less crowded environment and probably facilitates acylation. In addition, this distortion causes the C-1 carbon–oxygen bond to bisect the C-3 carbon–hydroxymethyl carbon bond.[29] This possibly exacerbates the steric interactions between the groups and decreases the relative reactivity of the C-3 hydroxymethyl toward acylation. This is a possible explanation for the observed regioselectivity of the acylation.

Although an X-ray structure of the diol **23** has not been done to confirm whether the same distortion is present, the result should be the same, since the pivaloyl group is relatively remote from the ring system and should exhibit little or no effect on the conformation.

Conclusion

The goal of obtaining a highly functionalized and stereochemically pure BC ring system for use in the synthesis of coriolin (**1**) has been achieved. Studies to convert the intermediate **25** to the coriolin (**1**) system are in progress.

Experimental Section

Proton NMR spectra were recorded on either a Varian EM 360A or XL 100 spectrometer, with Me_4Si as an internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 281 spectrophotometer. Melting points were obtained on a Mel-Temp melting point apparatus and are uncorrected. Flash chromatography refers to the method described by Still,[30] using E. Merck silica gel 60 (230–400 mesh). Thin-layer chromatography (TLC) was performed on E. Merck glass or aluminum foil supported silica gel 60 (0.25 mm, F-254). Silica gel for column chromatography

(27) Compound **30** was prepared from **16** in a manner identical with that shown for the ethyl carbonate in Scheme VII, by substituting β-(trimethylsilyl)ethyl chloroformate for ethyl chloroformate. Cf. Lipshutz, B.; Pegram, J. J. *Tetrahedron Lett.* **1980**, 3343 and references cited therein.

(28) Schomaker, V.; Waser, J.; Marsh, R. E.; Bergman, G. *Acta Crystallogr.* **1959**, *12*, 600.

(29) This effect can be most easily examined by using Dreiding molecular models. For an excellent discussion concerning the conformation of five-numbered rings, see Eliel, E. L. In "Stereochemistry of Carbon Compounds"; McGraw-Hill: New York, 1962; Chapter 9, p 248.

(30) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

was Baker reagent grade (60–200 mesh). Analyses for C and H were obtained by Dr. Franz Kasler of the University of Maryland. Alcohols **20** and **21** could not be obtained solvent free due to their viscous nature and were analyzed as the derived (acetic anhydride/pyridine) crystalline acetates. Acetylation (acetic anhydride/pyridine) was used to determine the number of free hydroxy groups present in some of the products.

Cyclopentanone ethylene ketal (9) was prepared by the method described by DePuy.[31] The ketal was obtained in 70% yield, bp 150–155 °C (lit.[31] 152–155 °C).

10,10-(Ethylenedioxy)-1α,2β,6β,7α-tricyclo[5.2.1.0^{2,6}]deca-4,8-dien-3-one (8). The methods of Chapman[17] and Paquette[18] for the preparation of the 3,10-diketal were modified. The crude 2,5-dibromocyclopentanone ethylene ketal (**10**; 314.7 g, ~15% dioxane by weight), obtained via bromination[17] (Br_2/dioxane) of cyclopentanone ethylene ketal (**9**; 128.2 g, 1.00 mol), in 600 mL of methanol was added over a 20-min period to a cold (5–10 °C) solution of sodium methoxide (324 g, 6.0 mol) in 1000 mL of methanol. The resulting black solution was refluxed under a N_2 atmosphere for 15 h, then cooled and poured into 7.5 L cold water. The black, aqueous solution was filtered through Celite, acidified by cautious addition of cold, concentrated aqueous HCl (pH 1–2), and allowed to stand for 15 min before extraction with 5 × 700 mL of CH_2Cl_2. The combined extracts were washed with water (2 × 250 mL), dried over $MgSO_4$, and concentrated to ~200 mL. The resulting viscous, black solution was diluted with 2 L of ether and filtered through a layer of Celite, and the filtrate was concentrated in vacuo to 87.2 g of waxy, tan crystals, which were recrystallized from ethanol to yield the enone **8** (60.3 g, 59%), mp 91–93 °C (lit.[27] 93–94 °C).

10,10-(Ethylenedioxy)-1α,2β,6β,7α-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-ol (12). Sodium borohydride (3.75 g, 99.0 mmol) was added in small portions to a solution of enone **8** (15.0 g, 73.4 mmol) in 125 mL of absolute ethanol, followed by stirring for 75 min at room temperature. The resulting ethanolic solution was concentrated in vacuo to ~30 mL, diluted with 150 mL of water, and extracted with CH_2Cl_2 (4 × 75 mL). The combined extracts were washed with water, dried over Na_2SO_4, and concentrated to a clear oil (15.73 g, 100%), which was pure by analytical TLC and was oxidized without further purification to the ketone **13** (vide infra): NMR ($CDCl_3$, 60 MHz) δ 1.10–1.90 (m, 4 H), 1.95 (br s, 1 H), 2.35–3.15 (m, 4 H), 3.85 (m, 4 H), 4.15–4.50 (m, 1 H), 6.10–6.55 (m, 2 H); IR (neat) 3400 cm^{-1}.

Pyridinium Chlorochromate (PCC) Oxidation of Alcohol 12. A slurry of PCC[19] (6.45 g, 30.0 mmol) and 12 g of Celite in 175 mL of CH_2Cl_2 was placed in a 1-L, three-necked, round-bottomed flask equipped with an addition funnel and a mechanical stirrer. The crude alcohol **12** (4.12 g, 19.8 mmol) in 50 mL of CH_2Cl_2 was added dropwise over a 30-min period, and the reaction mixture was stirred vigorously for 7 h at room temperature. The reaction mixture was diluted with 250 mL of ether, stirred for an additional 30 min, and then filtered through a short column of silica gel. After removal of all volatile solvents, the black residue was dissolved in 600 mL of ether, washed with 5% aqueous NaOH (2 × 50 mL), cold 5% aqueous HCl (2 × 50 mL), saturated aqueous $NaHCO_3$ (50 mL), and saturated aqueous NaCl (50 mL), dried over Na_2SO_4, and concentrated in vacuo to a yellow oil (2.96 g, 72%). The NMR spectra of the product was identical with that of the ketone **13** prepared by reduction of enone **8** with LiAlH(OMe)$_3$ (vide infra).

Reduction of Enone 8 with Lithium Trimethoxyaluminum Hydride/Cuprous Bromide. The procedure described by Semmelhack[23] for the reduction of α,β-unsaturated ketones was used. LiAlH(OMe)$_3$ (0.45 M, 12.0 mL, 5.4 mmol) in THF[22] was added via syringe to a suspension of anhydrous cuprous bromide (900 mg, 6.3 mmol) in 10 mL of THF maintained under N_2 atmosphere at 0 to −5 °C. The resulting black solution was stirred for 30 min and then cooled to −70 °C, and enone **8** (408.7 mg, 2.0 mmol) in 10 mL of THF was added rapidly. After 10 min, 10 mL of methanol was added, and the mixture was poured into 125 mL of saturated aqueous, NH_4Cl solution and then extracted with several portions of ether. The combined extracts were washed with water, dried over $MgSO_4$, and concentrated to yield the ketone **13** (348.1 mg, 84%): NMR ($CDCl_3$, 60 MHz) δ 1.25–2.40 (m, 4 H), 2.75–3.40 (m, 4 H), 3.88 (br s, 4 H), 6.26 (m, 2 H); IR ($CHCl_3$) 3010, 2980, 2950, 2880, 1725, cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.40; H, 7.00.

10,10-(Ethylenedioxy)-4,4-dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.0^{2,6}]dec-8-en-3-one (14). A solution of potassium *tert*-butoxide (19.45 g, 170 mmol) in 100 mL of *tert*-butyl alcohol was cooled to ~5 °C in a 250-mL, three-necked, round-bottomed flask equipped with a reflux condenser, a N_2 inlet, and an addition funnel. The ketone **13** (10.82 g, 52.5 mmol) in 50 mL of *tert*-butyl alcohol was added rapidly, followed by the immediate addition of methyl iodide (13.2 mL, 29.8 g, 210 mmol). Once the initial exothermic reaction had subsided, the solution was heated to reflux for 4.5 h, then cooled and poured into 300 mL of cold water. After the *tert*-butyl alcohol was removed under reduced pressure, the aqueous solution was extracted with ether (3 × 200 mL). The combined extracts were washed with water (2 × 75 mL) and saturated aqueous NaCl (75 mL), dried over $MgSO_4$, and concentrated in vacuo to a light yellow oil (10.49 g, 85%), which was used for subsequent reactions with no purification. A sample of the ketone was purified by flash chromatography (10% EtOAc/hexane eluant) to yield a clear oil, which crystallized slowly on standing: mp 32–33 °C; NMR ($CDCl_3$, 100 MHz) δ 0.88 (s, 3 H), 1.04 (s, 3 H), 1.23 (dd, 1 H, J = 13.2 and 7.3 Hz), 1.88 (dd, 1 H, J = 13.2 and 9.0 Hz), 2.78 (m, 1 H), 2.92 (m, 1 H), 3.00–3.41 (m, 2 H), 3.89 (m, 4 H), 6.06–6.22 (m, 2 H); IR ($CHCl_3$) 3060, 2960, 2940, 2890, 2870, 1728 cm^{-1}. Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.69; H, 7.95.

3α-Hydroxy-10,10-(ethylenedioxy)-4,4-dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.0^{2,6}]dec-8-ene (15). Sodium borohydride (160 mg, 4.2 mmol) was added to the dimethyl ketone **14** (481.7 mg, 2.06 mmol) in 10 mL of absolute ethanol, and the reaction mixture was stirred for several hours at room temperature. The ethanolic solution was concentrated under reduced pressure to ~1 mL, diluted to 10 mL with water, and extracted with 25 mL of CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, and concentrated to a clear oil (510 mg, 100%): NMR ($CDCl_3$, 60 MHz) δ 0.80–1.30 (m, 3 H), 0.91 (s, 3 H), 0.93 (s, 3 H), 2.55–3.25 (m, 4 H), 3.55–3.80 (m, 1 H), 3.87 (m, 4 H), 6.16 (br dd, 1 H, J = 6.5 and 3.0 Hz), 6.53 (br dd, 1 H, J = 6.5 and 3.0 Hz); IR ($CHCl_3$) 3570, 3050, 3000, 2950, 2880 cm^{-1}.

3α-Acetoxy-10,10-(ethylenedioxy)-4,4-dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.0^{2,6}]dec-8-ene (17). The endo alcohol **15** (279.4 mg, 1.18 mmol) was acylated by treatment with 6 mL of acetic anhydride in 6 mL of pyridine at room temperature for 16 h. After pyridine and excess acetic anhydride were removed under reduced pressure, the oily residue was purified by flash chromatography (20% EtOAc/hexane eluant) to yield the acetate **17** as waxy crystals (100%). Recrystallization from hexane gave 202.4 mg (61%): mp 84–86 °C; NMR ($CDCl_3$, 100 MHz) δ 0.86 (s, 3 H), 1.01 (s, 3 H), 1.05–1.40 (m, 2 H), 2.03 (s, 3 H), 2.58 (m, 2 H), 2.75–3.35 (m, 2 H), 2.86 (m, 2 H), 2.03 (s, 3 H), 2.58 (m, 2 H), 2.75–3.35 (m, 2 H), 2.86 (m, 4 H), 4.73 (d, 1 H, J = 6.6 Hz), 6.00–6.20 (m, 2 H); IR ($CHCl_3$) 3070, 3010, 2960, 2880, 1720 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 69.17; H, 8.20.

3β-Hydroxy-10,10-(ethylenedioxy)-4,4-dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.0^{2,6}]dec-8-ene (16). The dimethyl ketone **14** (10.49 g, 44.4 mmol) in 45 mL of ether and 125 mL of ethanol was placed in a 1-L, three-necked, round-bottomed flask equipped with an ammonia inlet, dry ice condenser, and a drying tube. Ammonia (~300 mL) was distilled into the reaction flask, and the rapidly stirred solution was treated with lithium metal (5.0 g, 0.72 mol), added in portions over 3.5 h. After cautious addition of 26 g of solid NH_4Cl and evaporation of the ammonia overnight, 400 mL of water was added, and the resulting mixture was extracted with CH_2Cl_2 (4 × 200 mL). The combined extracts were washed with water (2 × 50 mL) and saturated aqueous NaCl (75 mL), dried over Na_2SO_4, and concentrated in vacuo to 11.49 g. The crude product was purified by flash chromatography (10% EtOAc/hexanes eluant) to yield a viscous, pale yellow oil (7.00 g, 70%): NMR ($CDCl_3$ 100 MHz) δ 0.80–1.05 (m, 1 H), 0.88 (s, 3 H), 0.93 (s, 3 H), 1.45 (dd, 1 H, J = 11.8 and 8.0 Hz), 1.90 (br s, 1 H), 2.40–2.95 (m, 4 H), 3.15 (d, 1 H, J = 7.7 Hz), 3.86 (m, 4 H), 6.25–6.40 (m, 2 H); IR ($CHCl_3$) 3600, 3460, 3060, 3010, 2960, 2890 cm^{-1}.

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3β-Acetoxy-10,10-(ethylenedioxy)-4,4-dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.0^{2,6}]dec-8-ene (18). The exo alcohol **16** (0.85 g, 3.6 mmol) was acylated by treatment with 12 mL of acetic anhydride in 12 mL of pyridine (~12 h), followed by concentration in vacuo. This afforded a tan crystalline solid (1.00 g, 100%), which was triturated with cold hexane to yield the acetate **18** (0.45 g, 45%) as pale tan crystals: mp 91–92 °C; NMR ($CDCl_3$, 100 MHz) δ 0.80–1.05 (m, 1 H), 0.87 (s, 3 H), 1.00 (s, 3 H), 1.48 (dd, 1 H, J = 7.8 and 12.3 Hz), 2.05 (s, 3 H), 2.50–3.10 (m, 4 H), 3.85 (m, 4 H), 4.16 (d, 1 H, J = 7.4 Hz), 6.24 (br dd, 1 H, J = 3.5 and 6.5 Hz), 6.45 (br dd, 1 H, J = 3.0 and 6.5 Hz); IR ($CHCl_3$) 3060, 3010, 2980, 2890, 1730 cm^{-1}. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.95; H, 8.25.

3,3-(Ethylenedioxy)-2β,4β-bis(hydroxymethyl)-7,7-dimethyl-1α,5α-bicyclo[3.3.0]octan-6α-ol (19). The exo tricyclic alcohol **16** (3.11 g, 13.2 mmol) in 15 mL of CH_2Cl_2 and 100 mL of methanol was cooled to −70 °C, and O_3/O_2 was bubbled through the solution until a blue color persisted. Sodium borohydride (8.0 g, 0.21 mol) was added in small portions over a period of 1.5 h, and the reaction mixture was allowed to warm to room temperature. After hydrolysis with 30 mL of water and removal of solvents in vacuo, the resulting salts were triturated with several portions of warm ethyl acetate and filtered. The combined ethyl acetate solutions were dried over Na_2SO_4 and concentrated in vacuo to a viscous oil, which crystallized from ether/hexane to yield the triol **24**: mp 135–137 °C (2.84 g, 80%); NMR ($CDCl_3$, 100 MHz) δ 0.89 (s, 3 H), 1.03 (s, 3 H), 1.30–1.85 (m, 5 H, 3-OH), 2.20–2.95 (m, 4 H), 3.90–4.20 (m, 9 H); IR ($CHCl_3$) 3600, 3450, 3010, 2960, 2900 cm^{-1}. Anal. Calcd for $C_{14}H_{24}O_5$: C, 61.74; H, 8.88. Found: C, 61.46; H, 9.17.

Acetylation of Triol 19. The triol **19** (124 mg, 0.41 mmol) was treated with 6 mL of acetic anhydride in 6 mL of pyridine at room temperature for 16 h, followed by removal of pyridine and excess acetic anhydride under reduced pressure. The residual yellow oil was purified by flash chromatography (5% EtOAc/hexane eluant) to yield the triacetate as a clear oil (133 mg, 81%): NMR ($CDCl_3$, 100 MHz) δ 0.91 (s, 3 H), 0.96 (s, 3 H), 1.15–1.90 (m, 2 H), 2.01 (s, 3 H), 2.04 (s, 6 H), 2.27–2.95 (m, 4 H), 3.97 (m, 4 H), 3.95–4.35 (m, 4 H), 5.18 (d, 1 H, J = 7.5 Hz); IR ($CHCl_3$) 3030, 2965, 2900, 1735 cm^{-1}. Anal. Calcd for $C_{20}H_{30}O_8$: C, 60.29; H, 7.58. Found: C, 60.28; H, 7.80.

Reaction of Triol 19 with 2,2-Dimethoxypropane (DMP). The triol **19** (100.7 mg, 0.37 mmol) in 15 mL of CH_2Cl_2 was treated with DMP (7.0 mL, 55 mmol) and a catalytic amount (~1 mg) of pyridinium tosylate. After 24 h at room temperature, the reaction mixture was concentrated in vacuo, and the crude product was purified by column chromatography (10% EtOAc/hexane eluant) to yield a sticky oil (93.8 mg, 69%). The NMR and IR spectra indicated the presence of two acetonide moieties, and structure **21** was tentatively assigned. This product decomposed readily to yield the triol **19** and proved to be too unstable to obtain a satisfactory analysis: NMR ($CDCl_3$, 60 MHz) δ 0.83 (s, 3 H), 0.95 (s, 3 H), 1.00–1.60 (m, 2 H), 1.30 (s, 6 H), 1.35 (s, 6 H), 2.35–2.75 (m, 4 H), 3.11 (s, 3 H), 3.38 (d, 4 H, J = 6.0 Hz), 3.70–4.05 (m, 5 H); IR ($CHCl_3$) 2990, 2950, 2890, 2830 cm^{-1}.

10,10-(Ethylenedioxy)-4,4-dimethyl-1α,2β,6β,7α-tricyclo[5.2.1.0^{2,6}]dec-8-en-3β-yl Ethyl Carbonate (22). The exo-alcohol **16** (4.30 g, 18.2 mmol) in 100 mL of dry pyridine was cooled to 0 °C and treated with ethyl chloroformate (3.0 mL, 3.6 g, 29 mmol) added over 1.5 h. The pyridine and excess chloroformate were removed under reduced pressure, and the oily residue was dissolved in 200 mL of CH_2Cl_2, washed with cold 5% aqueous HCl (3 × 10 mL) and water (2 × 10 mL), dried over Na_2SO_4, and concentrated to a viscous oil, which was crystallized from hexane to give waxy crystals mp 50.5–52 °C (4.59 g, 80%): NMR ($CDCl_3$, 100 MHz) δ 0.86–1.65 (m, 2 H), 0.92 (s, 3 H), 1.02 (s, 3 H), 1.32 (t, 3 H, J = 7.1 Hz), 2.45–3.25 (m, 4 H), 3.86 (m, 4 H), 4.21 (d, 1 H, J = 6.9 Hz), 4.18 (q, 2 H, J = 7.1 Hz), 6.25 (br dd, 1 H, J = 6.3 and 3.0 Hz), 6.45 (br dd, 1 H, J = 6.3 and 2.8 Hz); IR ($CHCl_3$) 3060, 3030, 3010, 2980, 2960, 2890, 1735 cm^{-1}. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.26; H, 8.06.

3,3-(Ethylenedioxy)-2β,4β-bis(hydroxymethyl)-7,7-dimethyl-1α,5α-bicyclo[3.3.0]oct-6α-yl Ethyl Carbonate (23). The tricyclic ethyl carbonate **22** (2.77 g, 9.0 mmol) in 25 mL of CH_2Cl_2 and 100 mL of methanol was cooled to −70 °C, and O_3/O_2 was bubbled through until the solution turned pale blue. Excess O_3 was removed by bubbling oxygen through the solution for 10 min, and then 20 mL of dimethyl sulfide was added. The solution was stirred for 20 min and then treated with $NaBH_4$ (1.36 g, 36 mmol), added in small portions over 3 h. The reaction mixture was allowed to warm to room temperature, concentrated in vacuo to ~15 mL, diluted with 100 mL of water, and extracted with CH_2Cl_2 (5 × 60 mL); the extract was dried over Na_2SO_4 and concentrated in vacuo to a viscous oil, which crystallized from ether/hexane to yield 2.60 g (85%) of diol **23**: mp 138–140 °C; NMR ($CDCl_3$, 100 MHz) δ 0.93 (s, 3 H), 1.02 (s, 3 H), 0.85–1.80 (m, 2 H), 1.31 (t, 3 H), 1.69 (br s, 2 H), 2.10–2.60 (m, 2 H), 2.65–2.95 (m, 2 H), 3.78 (m, 4 H), 3.99 (br s, 4 H), 4.20 (q, 2 H), 5.00 (d, 1 H, J = 7 Hz); IR ($CHCl_3$) 3600, 3480, 3030, 3010, 2960, 2890, 1740 cm^{-1}. Anal. Calcd for $C_{17}H_{28}O_7$: C, 59.29; H, 8.19. Found: C, 59.29; H, 8.29.

Reaction of Diol 23 with Pivaloyl Chloride. The diol **23** (861 mg, 2.5 mmol) in 30 mL of anhydrous pyridine was cooled at −15 °C under a N_2 atmosphere and treated with 300 mg (2.5 mmol) of pivaloyl chloride, which was added slowly (~5 min) via syringe. The reaction mixture was maintained at −15 °C and treated with an additional 150 mg (1.8 mmol) of pivaloyl chloride, which was added in two portions at 16-h intervals.[32] After 48 h, methanol (2 mL) was added to consume any unreacted pivaloyl chloride, and the mixture was allowed to warm to room temperature. The resulting solution was concentrated in vacuo, and the oily residue was dissolved in 50 mL of ether. The ether solution was washed with saturated aqueous $NaHCO_3$ (3 × 5 mL), H_2O (2 × 5 mL), and cold 5% aqueous HCl (2 × 5 mL), dried over Na_2SO_4, and concentrated to a pale yellow oil (1.28 g), which was purified by flash column chromatography (5% EtOAc/hexanes gradually increased to 100% EtOAc eluant). The first product eluted was identified as the dipivalate ester **24** (197 mg, 15%), followed by monopivalate **25** (680 mg, 63%), monopivalate **26** (13.9 mg, 1.3%), and recovered diol **23** (183 mg, 21%). The recovered diol was treated in 6 mL of anhydrous pyridine at −15 °C with 225 mg (1.9 mmol, 3.5 equiv) of pivaloyl chloride, added over a period of 4 days, and then worked up as before and chromatographed to yield the dipivalate **24** (68.8 mg, 25%), monopivalate **25** (122 mg, 54%), monopivalate **26** (1.3 mg, 0.6%), and recovered diol **23** (20.9 mg, 11%). Total yield after recycle: dipivalate **24**, 265 mg (21%); monopivalate **25**, 80.2 mg (75%); monopivalate **26**, 15.2 mg (1.4%); diol **23**, 20.9 mg (2.4%). **24**: R_f 0.74 (3:2 EtOAc/hexane); mp 89–92 °C; NMR ($CDCl_3$, 100 MHz) δ 0.93 (s, 3 H), 1.01 (s, 3 H), 1.17 (s, 9 H), 1.18 (s, 9 H), 1.30 (t, 3 H, J = 7.1 Hz), 0.80–1.50 (m, 2 H), 2.25–2.90 (m, 4 H), 3.95 (m, 4 H), 4.05–4.30 (m, 6 H), 5.04 (d, 1 H, J = 7.5 Hz); IR ($CHCl_3$) 3010, 2960, 2900, 2870, 1740, 1725 cm^{-1}. **25**: R_f 0.58 (3:2 EtOAc/hexane); mp 127–129 °C; NMR ($CDCl_3$, 100 MHz) δ 0.94 (s, 3 H), 1.02 (s, 3 H), 1.19 (s, 9 H), 1.31 (t, 3 H, J = 7.1 Hz), 0.80–1.50 (m, 2 H), 2.05–2.90 (m, 5 H), 3.78 (dd, 2 H, J = 2.4 and 7.0 Hz), 3.97 (m, 4 H), 4.00–4.30 (m, 4 H), 5.05 (d, 1 H, J = 7.5 Hz); IR ($CHCl_3$) 3550, 3010, 2960, 2930, 2900, 2885, 1740, 1725, 1480, 1465, 1395, 1375, 1270, 1230, 1210, 1170, 1050, 1015, 970, 950 cm^{-1}.

X-ray Crystallographic Determination. Recrystallization of **25** from ether–hexane yielded colorless needles. A 0.15 × 0.15 × 0.55 mm crystal, mounted parallel to the needle axis (a), was used for all X-ray work. The cell dimensions and intensity data were measured on a Picker FACS-I diffractometer with graphite monochromated radiation (Cu Kα $\bar{\lambda}$ = 1.5418 Å). The cell constants were determined by least-squares from the +20 values of 18 automatically centered reflections. The space group and cell parameters are as follows: triclinic, $P\bar{1}$; a = 6.733 (6), b = 13.33 (2), c = 14.65 (2) Å, α = 71.07 (8), β = 88.42 (8), α = 78.10 (8)°, d_{calcd} = 1.17 g cm^{-3} for $C_{22}H_{36}O_8$ and Z = 2. The intensity data were measured with the $2\theta - \theta$ scan technique: 2° min^{-1} scan in 2θ, 2θ scan range = 1.6° + 0.29 tan θ, 2θ maximum of 126°, 10 s backgrounds. A total of 3938 unique reflections were obtained, of which 2581 were $\geq 3\sigma$ above background. The structure was solved with the MULTAN-80 system of direct methods programs,[33]

(32) The progress of this acylation reaction was closely monitored by TLC analysis (3:2 hexanes–EtOAc). In general, pivaloyl chloride was subsequently added as necessary to drive the reaction to near completion. If too much pivaloyl chloride was added at one time, this resulted in the formation of larger amounts of the dipivalate ester.

which revealed solid positions for 21 of the nonhydrogen atoms, followed by a few cycles of structure factor difference map calculations to locate the remaining atoms. The structure refinement used the method of full matrix, least-squares and minimized the function $\sum[1/\sigma(F)]^2(F_o - F_c)^2$. Hydrogen atoms were not included in the calculations. The final $R = (\sum||F_o| - |F_c||/\sum F_o)$ and with $R = ([[\sum w(|F_o| - |F_c|)^2]\sum wF_o^2]^{1/2}$, $w = [1/\sigma(F)]^2$) were 0.114 and 0.122.

All of the calculations were performed at the University's Computer Science Center on a UNIVAC 1100/40 computer. With the exception of the MULTAN-80 system, the crystallographic programs used were those of the X-ray system.[34]

26: R_f 0.54 (3:2 EtOAc/hexane); NMR ($CDCl_3$, 100 MHz) δ 0.94 (s, 3 H), 1.02 (s, 3 H), 1.18 (s, 9 H), 1.31 (t, 3 H, J = 7.2 Hz), 0.80–1.51 (m, 2 H), 2.05–2.85 (m, 5 H), 3.77 (d, 2 H, J = 7 Hz), 3.95 (m, 4 H), 3.90–4.30 (m, 4 H), 5.02 (d, 1 H, J = 7.5 Hz); IR ($CHCl_3$) 3500, 3030, 2960, 2930, 2870, 1730, 1480, 1460, 1410, 1390, 1275, 1225, 1160, 1070, 1010 cm^{-1}.

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Registry No. 1, 74183-95-2; 8, 62929-25-3; 9, 176-32-9; 10, 25834-57-5; 12, 82390-16-7; 13, 82468-23-3; 14, 82431-53-6; 15, 82431-54-7; 16, 82468-24-4; 17, 82431-55-8; 18, 82468-25-5; 19, 82431-56-9; 19 triacetate, 82431-57-0; 21, 82431-58-1; 22, 82431-59-2; 23, 82431-60-5; 24, 82431-61-6; 25, 82431-62-7; 26, 82431-63-8; 30, 82431-64-9; pivaloyl chloride, 3282-30-2; ethyl chloroformate, 541-41-3; β-(trimethylsilyl)ethyl chloroformate, 20160-60-5.

Supplementary Material Available: Atomic fractional coordinates and anisotropic temperature factors for compound **25** (2 pages). Ordering information is given on any current masthead page.

Glycol Ester Formation in the Reformatsky Reaction†

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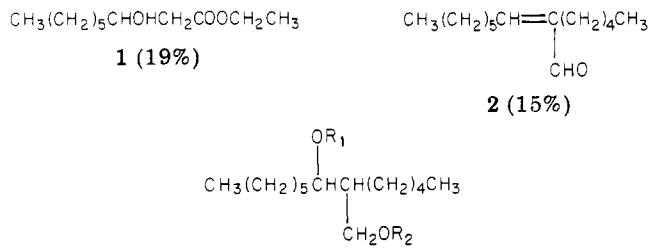
A previously unrecognized side reaction in the Reformatsky reaction has been identified in the reaction of heptanal with ethyl bromoacetate. The products are derived from the two isomeric heptanoates of the glycol 2-pentyl-3-hydroxynonanol, formed from 3 mol of heptanal under the presumed catalysis of the bromo zinc enolate.

The Reformatsky reaction of aliphatic aldehydes often gives low yields,[1-4] though improved procedures are now available.[5-12] In particular, the reaction of heptanal with ethyl bromoacetate has been reported to give only low yields of product[13] and this reaction is also one of the least satisfactory employing at least one of the improved procedures.[5] Moreover, heptanal also gives a relatively low yield with ethyl α-bromopropionate.[14] It has been observed that under a variety of reaction conditions,[1,15,16] a large amount of high-boiling material is formed which would not be expected from the known side reactions encountered in the Reformatsky reaction.[1,17,18] To explain the formation of these high-boiling products we have examined in detail the reaction of heptanal and ethyl bromoacetate and report here our results.

Standard Reformatsky conditions[15,19] were employed except that a twofold excess of heptanal was used to facilitate characterization of the high-boiling compounds. Thin-layer chromatographic analysis of the crude reaction product indicated the presence of approximately six compounds. Initial separation of the mixture was effected by vacuum distillation to yield volatile (44%) and nonvolatile (56%) fractions. The same products were detected by thin-layer chromatography (TLC) in two fractions after distillation, indicating no decomposition occurred during distillation. Both the volatile and the nonvolatile fractions were purified by silica gel chromatography, yielding compounds **1**–**6** in the proportions shown in parenthesis in Chart I.[20]

Chromatography of the volatile fraction gave two known compounds, the regular Reformatsky product, β-hydroxy ester **1**, and an expected byproduct, the dehydration product of the aldol of heptanal, **2**. Chromatographic

Chart I



3a, R_1 = H; R_2 = $CO(CH_2)_5CH_3$ (20%)
b, R_1 = $CO(CH_2)_5CH_3$; R_2 = H (5%)
4a, R_1 = $COCH_2Br$; R_2 = $CO(CH_2)_5CH_3$ (9%)
b, R_1 = $CO(CH_2)_5CH_3$; R_2 = $COCH_2Br$ (3%)
5a, R_1 = $COCH_3$; R_2 = $CO(CH_2)_5CH_3$ (3%)
b, R_1 = $CO(CH_2)_5CH_3$; R_2 = $COCH_3$ (<1%)
6a, R_1 = $COCH_2CHOH(CH_2)_5CH_3$; R_2 = $CO(CH_2)_5CH_3$
b, R_1 = $CO(CH_2)_5CH_3$; R_2 = $COCH_2CHOH(CH_2)_5CH_3$ } (7%)
7, R_1 = R_2 = H

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† To James Cason on his 70th birthday.

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