A Synthetic Approach to the Cis-Fused Marine Pyranopyrans, (3*E*)- and (3*Z*)-Dactomelyne. X-ray Structure of a Rare Organomercurial

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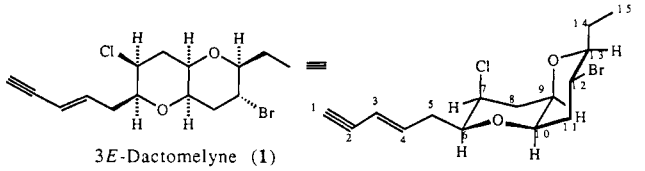
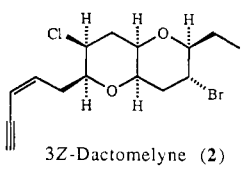
Investigations into the total synthesis of the unusual marine-derived pyranopyrans, the dactomelynes 1 and 2, are described. Present studies have led to the development of a scheme for procuring an appropriately functionalized bromine-containing pyranopyran **26**. This intermediate was assembled by the application of the oxymercuration reaction to the olefinic alcohol **6**. A single-crystal X-ray analysis has been obtained for the rare "basket-shaped" organomercurial **23b** which served to define the stereochemistry of the tricyclic product **5**.

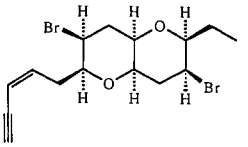
The structurally unusual cis-fused pyranopyrans **1** and **2** have been recently isolated from the digestive glands of the sea hare *Aplysia dactylomela* by Schmitz et al. These compounds, which differ only in the geometry of their C-3, C-4 double bonds, have been designated (3*E*)- and (3*Z*)-dactomelyne.[1] The structure of (3*E*)-dactomelyne including its absolute stereochemistry has been secured by X-ray analysis. The absolute configurations of its stereogenic centers C-6, C-7, C-12, and C-13 are *S*, *S*, *R*, and *S*, respectively. The structure of (3*Z*)-dactomelyne is solidly based upon spectral comparisons with **1**.[1]



3*E*-Dactomelyne (**1**)



3*Z*-Dactomelyne (**2**)



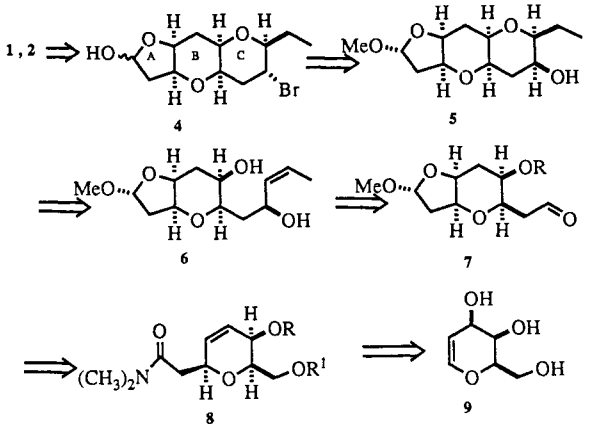
Elatenyne (**3**)

A report in 1986 by Hall and Reiss has revealed the existence of a closely related (pyranopyranyl)vinylacetylene, elatenyne (**3**), which was obtained from a sample of *Laurencia elata*.[2] The dactomelynes and elatenyne represent a group of nonisoprenoid, halogenated ethers which are characterized by an unbranched 15 carbon backbone containing a conjugated enyne terminus.

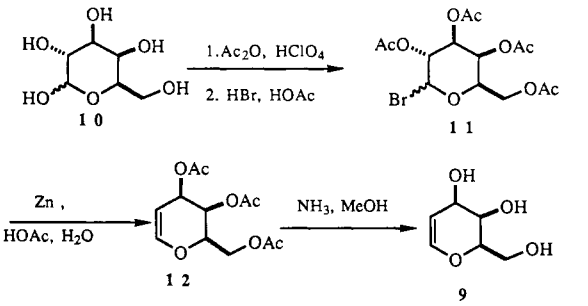
The structural uniqueness of these products in addition to their as yet unknown biological function make them attractive targets for synthesis in the laboratory. Since the dactomelynes were isolated in very minute quantities, a laboratory synthesis would provide the quantities of material needed to evaluate these compounds pharmacologically.

In this paper we describe our efforts to gain access by synthesis to these compounds. Our retrosynthetic analysis of the dactomelynes is shown in Scheme I. In our analysis of these compounds particular attention was paid to the presence of the cis ring fusion of the pyranopyran system as well as to the existence of the C-7 axial chlorine atom and the C-12 equatorial bromine atom. We anticipated that **1** and **2** could be derived from the lactol **4** by Wittig chemistry and chlorination with retention of configuration.

Scheme I. Retrosynthetic Analysis of the Dactomelynes



Scheme II. Improved Route to D-Galactal



The bromide **4** could come from the hydroxypyran **5** through bromination of the alcohol. The tricyclic system **5** might in turn be procured from the olefinic diol **6**, available from **7** by a chelation controlled Grignard addition reaction to its aldehyde group. Ultimately, we envisioned that D-galactal (**9**) would serve as a suitable precursor to **7** by way of a Claisen rearrangement process to give **8** coupled with a subsequent lactonization step and homologation of the C-6 (galactal numbering) hydroxyl group.[3]

Synthetic Results

While D-galactal is available commercially, the price of this starting material is somewhat exhorbitant. Accordingly, we have modified known procedures to enable us to procure **9** on the multigram scale.[4,5] D-Galatose **10** was converted to D-galactose pentaacetate by reaction with

(1) Gopichand, Y.; Schmitz, F. J.; Shelly, J.; Rahman, A.; van der Helm, D. *J. Org. Chem.* **1981**, *46*, 5192.
(2) Hall, J. G.; Reiss, J. A. *Aust. J. Chem.* **1986**, *39*, 1401.
(3) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon Press: New York, 1983.
(4) Levene, P. A.; Tipson, R. S. *J. Biol. Chem.* **1931**, *93*, 631.
(5) Jeanloz, R. W.; Stoffyn, P. *J. Methods Carbonhydr. Chem.* **1962**, *2*, 224.

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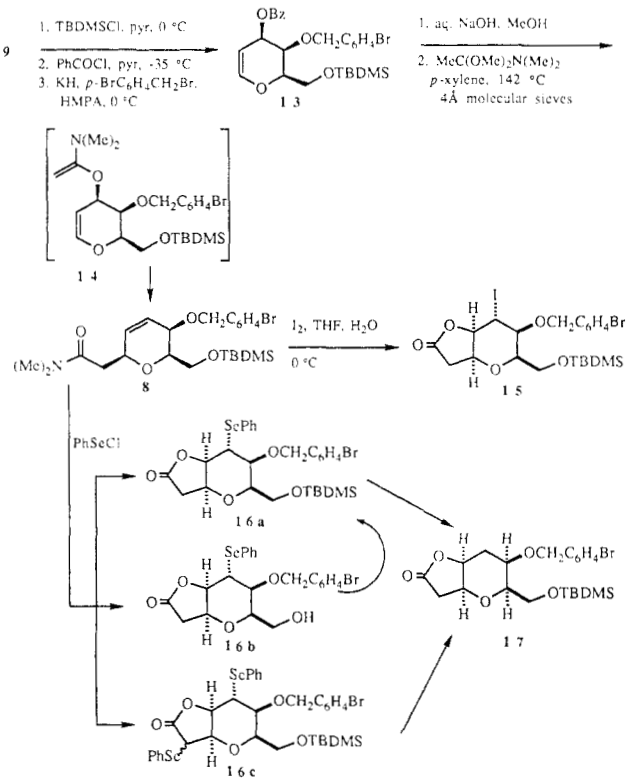
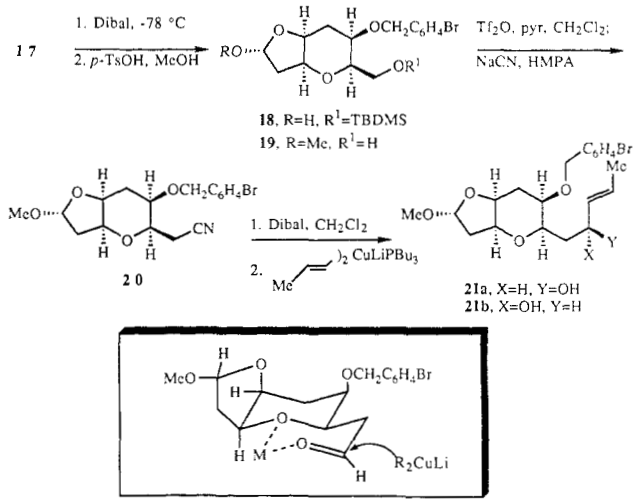
Scheme III. Preparation of Lactone 17



Scheme IV. Elaboration of 17 to Allylic Alcohol 21a



acetic anhydride in the presence of a catalytic amount of 70% perchloric acid (Scheme II). The crude product was converted directly to the bromide **11** by treatment with 30% HBr in acetic acid at 23 °C for 1.5 h. The crude bromide was subjected, in turn, to reductive elimination with zinc in aquous acetic acid at −20 °C to yield **12**. While cleavage of the acetate groups from **12** was attempted using several standard procedures (e.g., $Ba(OH)_2$ in MeOH; Et_3N/H_2O/MeOH; NaOMe in MeOH),[6] the use of ammonia in methanol worked best. Lastly, the crude galactal was crystallized from ethyl acetate, washed successively with methylene chloride and ether, and dried in vacuo to afford the nonodorous product **9** of mp 89–91 °C.[4,6] This procedure has been carried out on the 0.5-mol scale and proceeds in ~58% overall yield.

With gram quantities of the now readily available galactal in hand, we could proceed with the study of its conversion to **8**. The primary hydroxyl group was selectively silylated, and the allylic hydroxyl group was then protected by benzoylation with benzoyl chloride in pyridine at −35 °C. Next, the remaining hydroxyl group was protected as its *p*-bromobenzyl ether[7] under carefully monitored conditions, employing potassium hydride as base (1.4 equiv) in dry HMPA at 0 °C. The *p*-bromobenzyl protecting group was chosen with the notion that its deprotection could be coupled with concomitant formation of the C ring of **4** (Scheme I) through the iodocyclization reaction.[8] The benzoate group of **13** was removed by hydrolysis with aqueous sodium hydroxide in methanol.

The resulting product was now subjected to the Eschenmoser–Claisen rearrangement[9] reaction by heating with *N,N*-dimethylacetamide dimethyl acetal in *p*-xylene at 145 °C for 4 h to give **8** in 60% yield along with unreacted starting material. The yield could be improved considerably (~95%) by equipping the reaction flask with a Soxhlet apparatus containing 4-Å molecular sieves to remove the methanol from the reaction mixture. In this fashion the rearrangement reaction has been run reproducibly on a 10-g scale (Scheme III).

Treatment of the amide **8** with 3 equiv of iodine in $THF-H_2O$ (1:1) at 0 °C for 1.5 h afforded the desired iodo lactone **15** in but 40% yield together with the starting amide (~60%).[10] Since this yield was rather modest, we required a more effective method for lactonization in order to circumvent a tedious recycling procedure. While the use of N,N-disubstituted amides in selenium-induced cyclization reactions was unexplored, we subjected **8** to phenylselenenyl chloride in methylene chloride at −78 °C.[8,11] After 2 h, the reaction mixture was quenched with aqueous sodium bicarbonate, and the products were separated by chromatography to afford **16a** (86%), **16b** (4%), and **16c** (2%). The structures of **16b** and **16c** were identified on the basis of their NMR and mass spectral data and were further confirmed by subsequent chemical transformations. Lactone **16b** was converted to **16a** by silylation, while the diselenylated lactone **16c** was transformed to **17** by the action of *n*-Bu_3SnH in toluene. The major product of the selenylation reaction was likewise transformed to **17** by *n*-Bu_3SnH in toluene at 110 °C (90% yield).[12] Since the minor products of the selenylation reaction could be transformed to usable products, no further attempts were made to optimize the reaction conditions for the selenolactonization reaction.

The selenolactonization reaction is believed to take place by way of an imidate salt based upon the R_f of an intermediate detected by thin-layer chromatography, as well as the downfield shift of the *N*-methyl signals in the ^1H NMR spectrum of this intermediate relative to those of

(6) Czernecki, S.; Vijayakumaran, K.; Ville, G. *J. Org. Chem.* **1986**, *51*, 5472. For the methanolysis of tri-*O*-acetylgalactal an anion-exchange resin (Amberlite IRN-78, OH^- form) was used.

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(9) Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425; **1969**, *52*, 1030. For other examples of the glycal Claisen rearrangement, see: Fraser-Reid, B.; Dawe, R. D.; Tulshian, D. B. *Can. J. Chem.* **1979**, *57*, 1746. Fleet, G. W. J.; Gough, M. J.; Shing, T. K. M. *Tetrahedron Lett.* **1983**, *24*, 3661 and references cited therein.

(10) Corey, E. J.; Shibasaki, M.; Knolle, J. *Tetrahedron Lett.* **1977**, 1625.

(11) Nicolaou, K. C.; Magolda, R. L.; Sipio, J. W.; Barnette, W. E.; Lysenko, Z.; Joullie, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 3784. Nicolaou, K. C.; Seitz, S. P.; Sipio, W. J.; Blount, J. F. *J. Am. Chem. Soc.* **1979**, *101*, 3884.

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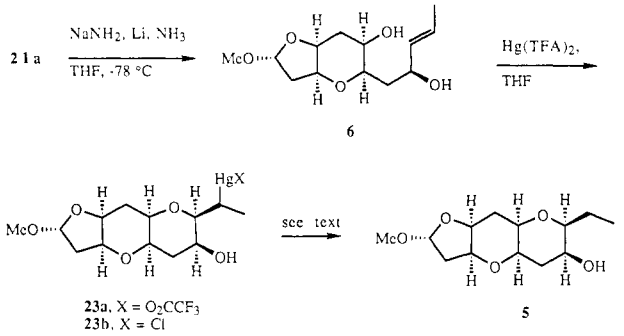
Scheme V. Conversion of 21a to the Pyranopyran 5 by an Oxymercuration Reaction



the starting amide (amide resonances 2.86 and 3.02 ppm; imidate salt resonances 3.32 and 3.52 ppm; spectra in acetone-d_6).[13] Exclusive formation of the lactone upon imidate hydrolysis can be explained by stereoelectronic effects.[14]

Next, the lactone **17** was reduced to lactol **18** by Dibal treatment. After an extractive workup, the lactol was treated with *p*-TsOH in methanol to afford the methyl glycoside **19** in 75% yield as a 5:1 mixture of anomers (the major isomer is depicted in Scheme IV). Following Scheme I (see intermediate **7**) required that the hydroxymethyl appendage of **19** be homologated by a single-carbon atom. The free hydroxyl group of **19** was thus activated for a cyanide displacement reaction by conversion to its tosylate, mesylate, iodide, nosylate, or triflate. Under a variety of conditions, only the unstable triflate was found to give rise to good yields of **20**.[15] The homologation step was carried out as a single-pot operation by treating the alcohol first with Tf_2O in CH_2Cl_2 in the presence of pyridine at −42 °C to provide the unstable triflate. After 5 min, powdered sodium cyanide and HMPA were added to the reaction mixture. In this fashion, a good yield (67–78%) of the nitrile **20** could be isolated.

This nitrile was next reduced with Dibal in methylene chloride to the corresponding aldehyde (77%). Addition of the cuprate reagent (3 equiv) derived from *trans*-1-propenyllithium[16] to this aldehyde proceeded in high chemical yield and with good stereoselection to afford a 7.3:1 ratio of **21a** and **21b**, respectively. The good level of 1,3-asymmetric induction observed is a likely consequence of metal chelation of the aldehyde carbonyl group to the pyran ring oxygen during the addition step.[17,18] The assignment of *S* stereochemistry to this newly created chiral center rests upon an X-ray analysis carried out on a subsequently derived organomercurial (vide infra).

With allylic alcohol **21a** in hand, we could now explore the crucial pyranoannulation reaction. While at the outset of our work we had expected that **21** might undergo an iodoetherification reaction with rupture of the benzyl ether protecting group, treatment of **21a** with iodine according

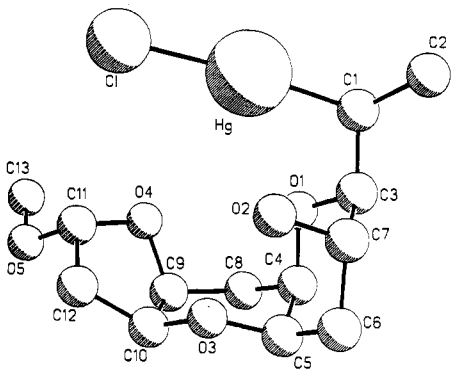


Figure 1. A computer-generated perspective drawing of **23b** obtained by single-crystal X-ray analysis.

to Bartlett's procedure led, in fact, to a complex mixture of products.[19] The *p*-bromobenzyl ether group of **21a** was thus removed by the action of lithium in ammonia. In order to preclude cleavage of the allylic hydroxyl group by these reductive conditions, deprotonation of the alcohol by sodium amide was effected prior to the addition of the lithium metal.[20] In this manner, a reproducible 93% yield of **6** was generated (Scheme V).

Diol **6** was treated with mercuric trifluoroacetate in THF, and the resulting mercurial **23a** was directly reduced with sodium borohydride. In this fashion the hydroxy pyranopyran **5** was isolated in 40% yield along with the epimeric pyranopyran (6%) and recovered starting material (44%).

Due to the ambiguity in rigorously assigning stereochemistry to **5** by NMR, its structure was deduced by the following sequence of chemical reactions: (a) oxidation of **5** with PCC; (b) epimerization with DBU in methanol (23–45 °C); (c) selective reduction with L-Selectride (Aldrich). These three steps led to the starting pyranopyran **5**. We can thus conclude that the ethyl group must occupy the thermodynamically favored equatorial position, while the alcohol occupies the axial position. Molecular mechanics calculations performed using the MM2 force field available in MacroModel (Version 2.0) indicated that the ketone derived from **5** bearing an equatorial ethyl group was approximately 3.3 kcal/mol lower in energy than the axial ethyl bearing isomer. The relative stereochemistry of **5** was further confirmed by an X-ray crystallographic analysis of the rare organomercurial **23b**. The mercurial chloride was obtained from **23a** by treatment with an aqueous KCl solution, extraction, and chromatography on silica gel. Monoclinic crystals were obtained by crystallization of the resulting solid from a hexane–ether mixture [mp 183–186 °C dec; density 2.16].

A computer-generated perspective drawing of **23b** is provided in Figure 1. In general, the bond distances and angles of the pyranopyran moiety are close to those commonly observed for the chair conformation of 6-membered rings. Interestingly, in this structure, the large mercury atom is situated above the electron-rich nest of oxygen atoms.

The high degree of stereoselectivity observed in the mercury(II)-induced pyranoannulation process can be rationalized in terms of a preference for a chairlike transition state **24** with the hydroxyl group assuming an axial position, and the emerging bulky alkylmercurial group the equatorial position.[8]

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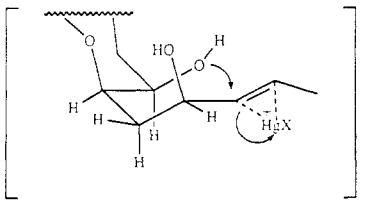


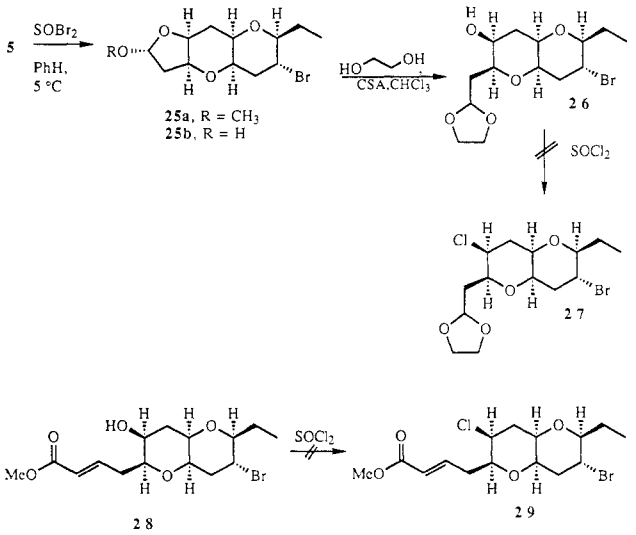
24

Demercuration of the alkoxymercuration product **23** did present initially certain difficulties (ca. 40% yield). One problem common to such reactions is elimination to the starting olefin. The success of such reductions is known to be highly dependent on the pH of the reaction mixture, the mercury ligand, and the reaction solvent.[21,22] Consequently, various alternative procedures have been developed for demercuration which include the use of LAH,[23] Ph_3SnH,[23] hydrazine,[24] hydrogen sulfide,[25] and $NaBH_4$ in a biphasic solvent system.[26] These modified reduction conditions were applied to **23**. However, the yields of product were generally low, and the methods appeared to offer no real advantages over the use of $NaBH_4$. After additional studies, we eventually found that the demercuration of the chloromercurio derivative **23b** could be accomplished in 57% yield by using tributyltin hydride in toluene in the presence of sodium acetate.[27] A further 8% improvement in the overall yield of **5** was attained by employing a two-step protocol consisting of homolytic conversion of the mercurial **23a** to bromide by pyridinium bromide perbromide treatment[28] followed by reduction of the bromide with tributyltin hydride.

During our studies of the optimization of the demercuration reaction, we also studied briefly the cyclization of **6** using a number of other electrophiles (NBS, NIS, *N*-(phenylseleno)phthalimide,[29] PhSeCl, and iodonium dicollidine perchlorate[30]). These cyclization processes were found to offer no advantages over the oxymercuration reaction, particularly in view of the stereo- and regioselectivity observed for the latter process.

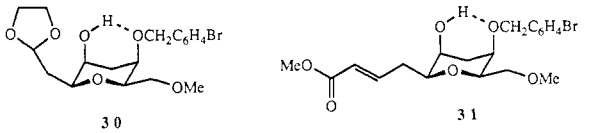
With the hydroxypyranopyran **5** in hand, the replacement of the hydroxyl group by a bromine atom could now be studied. A host of methods for accomplishing this transformation were investigated which included the use of Ph_3P/NBS,[31] Ph_3P/CBr_4,[32] $Ph_3P/DEAD/ZnBr_2$,[33] Ph_3P/tribromoimidazole,[34] PBr_3,[35] Tf_2O/Br^-,[36] $MsCl/Br^-$,[37] etc. Eventually we found that treatment of **5** with freshly distilled thionyl bromide (1.2 equiv) in benzene at 5 °C for 45 min followed by an aqueous $NaHCO_3$ workup provided bromide **25a** and the bromolactol **25b** in a ratio of

Scheme VI. Further Transformations of 5



1.5:1 in 65% yield (Scheme VI). Cleavage of the methyl glycoside linkage of **25a** by the action of 10% HCl in THF provided access to the pure lactol **25b**. The mixture of **25a** and **25b** was also reacted with ethylene glycol and camphorsulfonic acid in $CHCl_3$ at 50 °C to provide the ethylene acetal **26**. Unfortunately, the direct chlorination of **26** using thionyl chloride under a variety of conditions proved unsuccessful. Because the acetal group of **26** was found to be labile to acid, we also prepared the unsaturated ester **28** from **25b** by standard Wittig chemistry, and examined its reactivity with $SOCl_2$. However, even at temperatures of 100 °C in dioxane as solvent, only starting material was recovered along with trace amounts of the dehydration product. None of the chloride **29** could be detected.

Due to the time and expense of procuring large amounts of the alcohols **26** and **28** needed for the chlorination studies, we chose to employ the more readily available galactal-derived compounds **30** and **31** as model substrates. A range of strategies were examined for introduction of the chlorine atom which included inter alia, attempted geminal dichloride formation followed by elimination or reduction of one of the halogen atoms, olefin formation, and subsequent electrophilic addition reactions (X^+Cl^-), as well as the preparation of the inverted alcohol followed by chlorination with inversion. None of these studies, however, provided any glimmer of success.



30 31

Eventually, we considered the possibility of carrying out the chlorination step by a Barton type of radical-mediated replacement reaction on an xanthate ester.[38] Menthol was chosen as a test substrate, for its hydroxyl group is somewhat hindered as indicated by the failure to undergo a Mitsunobu type chlorination reaction (Ph_3P, DEAD, LiCl).[39] The xanthate ester **32** was thus treated with hexabutyldistannane and AIBN in CCl_4 at 110 °C in toluene or with NCS in place of the distannane.[40] Only

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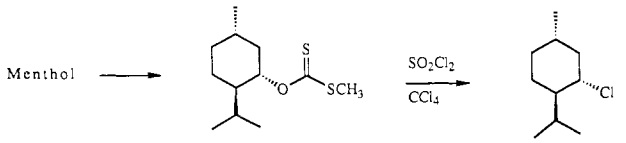
(39) Manna, S.; Falck, J. R.; Mioskowski, C. *Synth. Commun.* **1985**, *15*, 663.

starting material was recovered from these reactions. In contrast, when **32** was reacted with sulfuryl chloride (2.2 equiv) in CCl_4 at 0 °C to room temperature, menthyl chloride (**33**) was obtained in 82% yield. This reaction was found to proceed with retention of stereochemistry as evidenced by comparison of its NMR spectrum with that of menthol and an authentic sample of menthyl chloride.



32 33

This chlorination method was studied employing a number of other substrates. The reaction was found to proceed in good yield and with retention of stereochemistry as described in a recent publication.[41] The xanthate ester of **30** could, in fact, be converted to its axial chloride in 91% yield using SO_2Cl_2 in $CHCl_3$.

Unfortunately, when this newly discovered chlorination procedure was tried on the dactomelyne intermediate **26** under a plethora of experimental conditions, none of the desired chloride could be isolated. Apparently, this alcohol represents a greater extreme in steric congestion than is found in the model compound **30**.

In light of the foregoing difficulties, we have been forced to modify our overall approach to the dactomelynes. These new studies which make use of a chlorodihydropyran intermediate will be reported in due course. In summary, a workable route to a highly functionalized pyranopyran intermediate by way of a stereoselective intramolecular oxymercuration reaction has been developed en route to the dactomelynes.[42]

Experimental Section

General Procedures. Infrared spectra were obtained on an IBM IR/32 FTIR spectrometer. Spectra were obtained as neat films. ^1H NMR were recorded at 300 MHz (Bruker WH-300) in the solvent(s) noted.

Chemical shifts (δ) were reported with Me_4Si (δ = 0.000 ppm) or $CHCl_3$ (δ = 7.26 ppm) as internal standards. The following abbreviations are used: br = broad, d = doublet, m = multiplet, q = quartet, s = singlet, t = triplet. Low-resolution and high-resolution mass spectra were determined on a VG 70-SE double-focusing magnetic sector mass spectrometer at an ionizing potential of 15 or 70 eV.

Melting point were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected.

Silica gel 60 (Merck, 70–230 mesh or 230–400 mesh for flash chromatography) was used for column chromatography. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F-254 (0.25 mm, precoated on glass).

Visualization of compounds on TLC was accomplished by UV illumination or by staining with a solution prepared from 25 g of ammonium molybdate and 1 g of ceric sulfate in 500 mL of 10% sulfuric acid, followed by heating.

Distilled reagent-grade solvents were used for chromatography and extraction. Benzene and toluene were distilled from calcium hydride. Tetrahydrofuran (THF) and ether were distilled from sodium benzophenone ketyl. Methylene chloride and *p*-xylene were dried by passage through a column of activity 1 neutral alumina and stored over 4-Å molecular sieves. Dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) were distilled from calcium hydride under reduced pressure and stored over 4-Å molecular sieves. Pyridine was distilled from calcium oxide and stored over 4-Å molecular sieves.

Other solvents were used as supplied or purified as noted. All reactions were carried out in oven or flame-dried glassware with magnetic stirring unless noted otherwise.

Solutions and liquids were delivered by syringe or cannula through rubber septa or by pressure-equalizing dropping funnels where appropriate.

D-Galactal (9). A stirred suspension of 0.5 g of D-galactose (**10**) in acetic anhydride (300 mL) was treated dropwise with 1.8 mL of 70% perchloric acid. Additional D-galactose (75 g, 0.42 mol) was added in small portions over a period of 1.5 h. During the addition, the reaction mixture was maintained at 40 °C by occasional cooling in an ice–water bath. After addition was complete, the solution was cooled to 23 °C, and 330 mL of 30% HBr in acetic acid was added. After 1.5 h at room temperature, the reaction mixture was diluted with 700 mL of methylene chloride, and washed successively with ice–water (2 × 200 mL) and cold 5% aqueous $NaHCO_3$. The dried (Na_2SO_4) organic phase was concentrated to afford a syrup (**11**), R_f 0.64 (silica gel, 50% ethyl acetate–hexane).

This syrup was added slowly over a period of 1 h to 190 g of zinc dust in 1200 mL of 50% aqueous acetic acid with mechanical stirring while maintaining the temperature at −15 °C to −20 °C (dry ice/acetonitrile bath).

After addition was complete, the reaction mixture was stirred for an additional 1 h at 0 °C, and then the reaction mixture was filtered. The filtrate was diluted with methylene chloride (800 mL) and extracted with ice–water (3 × 250 mL). The organic extract was washed with cold saturated $NaHCO_3$ (2 × 200 mL) and saturated brine. The dried (Na_2SO_4) solution was concentrated below 40 °C to give 110 g of a white syrup: R_f 0.68 (silica gel, 50% ethyl acetate–hexane).

The crude tri-*O*-acetylgalactal (**12**) was dissolved in 600 mL of anhydrous methanol, and ammonia was bubbled through the solution at 0 °C for 3 h. The reaction mixture was then maintained at room temperature for 15 h. Concentration of the methanolic solution afforded a yellow syrup. The D-galactal (**9**) which crystallized from ethyl acetate was washed successively with methylene chloride (15 mL) and ether (40 mL): yield, 34.3 g (56% from D-galactose); mp 89–91 °C. (lit.[8] mp 100 °C).

6-*O*-(*tert*-Butyldimethylsilyl)-D-galactal. To a stirred solution of 15.5 g (0.106 mol) of D-galactal (**9**) in 155 mL of dry pyridine cooled to 0 °C under N_2 was added 17.58 g (0.116 mol) of *tert*-butyldimethylsilyl chloride in three portions over 1 h. One hour after the last addition, the resulting mixture was stirred at room temperature for 15 h, poured into 200 mL of 5% aqueous $NaHCO_3$, and extracted with two 200-mL portions of ethyl acetate. After the combined extracts were dried (Na_2SO_4), the solvent was removed under reduced pressure, and the pyridine was azeotropically removed by the addition of *n*-heptane followed by concentration under reduced pressure. Flash chromatography of the residue on silica gel with 1:1 ethyl acetate–hexane afforded 20.0 g (73%) of the monosilylated diol as a colorless oil: R_f 0.72 (silica gel, ethyl acetate); IR (thin film) 3395, 2953, 1464, 1255, 1105, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.12 (s, 6 H), 0.91 (s, 9 H), 2.71 (d, 1 H, J = 10.2 Hz), 3.20 (d, 1 H, J = 5.03 Hz) 3.88–4.01 (m, 3 H), 4.11 (br, 1 H, J = 6.13, 1.34 Hz), 4.32 (m, 1 H), 4.73 (m, 1 H), 6.38 (dd, 2 H, J = 6.18, 1.33 Hz); MS (70 eV) m/z 227, 203, 185 (M^+ − *t*-Bu − H_2O) 167, 155, 129, 117; HRMS calcd for $C_8H_{13}O_3Si$ 185.0634, found 185.0634.

3-*O*-Benzoyl-6-*O*-(*tert*-butyldimethylsilyl)-D-galactal. To a stirred solution of 20.0 g (76.89 mmol) of the above diol in 180 mL of dry pyridine cooled to −35 °C under N_2 was added 8.93 mL (79.89 mmol) of benzoyl chloride over 15 min. After 1.5 h, the mixture was allowed to warm to 0 °C for 30 min. A saturated solution of $NaHCO_3$ was added, and the resulting mixture was extracted with ethyl acetate (3 × 150 mL). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated by rotary evaporation. Azeotropic removal of pyridine with *n*-heptane (2 × 30 mL) followed by flash chromatography of the residue on silica gel with hexane–ethyl acetate (4:1) as eluent afforded 26.6 g (95%) of the benzoate as a colorless oil; R_f 0.70 (silica gel, 25% ethyl acetate–hexane); IR (thin film) 3400, 3034, 2928, 1730, 1275, 1101, 839 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.11 (s, 6 H), 0.91 (s, 9 H),

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2.97 (d, 1 H, J = 4.58 Hz), 3.91–4.04 (m, 4 H), 4.42 (br, 1 H), 4.81 (ddd, 1 H, J = 6.18, 1.9, 1.9 Hz), 5.68 (m, 1 H), 6.53 (dd, 1 H, J = 6.18, 1.51 Hz), 7.41–7.60 (m, 3 H), 8.10 (m, 2 H); MS (70 eV) m/z 307 (M^+ – t-Bu), 227, 201, 185, 117, 105; HRMS calcd for $C_{15}H_{19}O_5Si$ 307.1002, found 307.1001.

4-*O*-(4′-Bromobenzyl)-6-*O*-(*tert*-butyldimethylsilyl)-D-galactal. To a stirred, ice-cooled solution of 9.0 g (24.72 mmol) of the above hydroxy ester in 140 mL of dry HMPA was added 1.38 g (34.62 mmol) of potassium hydride and 6.80 g (27.19 mmol) of 4-bromobenzyl bromide. The potassium hydride dispersion was activated by washing twice with dry hexane and once with n-pentane. The reaction mixture was stirred at 0 °C for 1.5 h under N_2, and then 15 mL of water was added cautiously. The resulting mixture was diluted with 5% aqueous $NaHCO_3$ (150 mL) and extracted with ether (3 × 150 mL). The combined organic fractions were backwashed with 5% aqueous $NaHCO_3$, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow oil (**13**).

The crude product was passed through a small plug of silica gel with hexane–ethyl acetate (4:1) as the eluent. The materal obtained was used directly in the next reaction without further purification. The above mixture in 250 mL of methanol was treated with 12 mL of a 10% aqueous NaOH solution. After the mixture was stirred at room temperature for 15 h, the methanol was removed by rotary evaporation, and the residue was diluted with 50 mL of saturated aqueous NH_4Cl, and extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine and dried (Na_2SO_4). After removal of solvent under reduced pressure, flash chromatography of the residue over silica gel with hexane–ethyl acetate (4:1) afford 8.28 g (78.0%) of the allylic alcohol as an oil: R_f 0.42 (silica gel, 25% ethyl acetate–hexane); ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 6 H), 0.90 (s, 9 H), 2.57 (d, 1 H, J = 10.47 Hz), 3.74–3.80 (dd, 1 H, J = 10.42, 6.80 Hz), 3.87–4.00 (m, 3 H), 4.32 (m, 1 H), 4.73 (m, 3 H), 6.32 (dd, 1 H, J = 6.20, 1.39 Hz), 7.24 (d, 2 H, J = 12.4 Hz), 7.48 (d, 2 H, J = 12.4 Hz); MS (70 eV) m/z 429 (M^+), 369, 329, 317, 301, 267, 171; HRMS calcd for $C_{11}H_{14}O_3{}^{79}BrSi$ 300.9895, found 300.9899.

***N*,*N*-Dimethyl-(2*S*,5*R*,6*R*)-5-[(4′-bromobenzyl)oxy]-6-[[[(1,1-dimethylethyl)dimethylsilyl]oxy]methyl]-3,4-dideoxypyran-2-acetamide (8).** A solution of the allylic alcohol (6.30 g, 14.66 mmol) and *N*,*N*-dimethylacetamide dimethyl acetal (5.90 mL, 36.65 mmol) in dry p-xylene (65 mL) was heated under a N_2 atmosphere to 142 °C (bath temperature) and maintained at this temperature for 10 h. During this time, the mechanol was removed from the reaction mixture by using a Soxhlet apparatus containing 4-Å molecular sieves. Evaporation of p-xylene followed by chromatography of the reaction mixture on silica gel with hexane–ethyl acetate (3:1 to 1:1) afforded 6.94 g (95.0%) of the amide **8** as an oil: R_f 0.26 (silica gel, 50% ethyl acetate–hexane); IR (thin film) 3034, 2928, 1469, 1487, 1400, 1253, 1101, 839 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.06 (s, 6 H), 0.89 (s, 9 H), 2.49 (dd, 1 H, J = 14.0, 7.56 Hz), 2.74 (dd, 1 H, J = 14.0, 6.18 Hz), 2.95 (s, 3 H), 3.00 (s, 3 H), 3.60–4.90 (m, 4 H), 4.65–4.80 (m, 3 H), 5.60–6.00 (m, 1 H), 6.07–6.10 (dd, 1 H, J = 10.31, 1.08 Hz), 7.22 (d, 1 H, J = 8.29 Hz), 7.45 (d, 1 H, J = 8.29 Hz); MS (70 eV) m/z 440, 442 (M^+ – t-Bu), 324, 313, 254, 180, 166; HRMS calcd for $C_{15}H_{19}O_5Si$ 307.1002, found 307.1001.

(1*S*,3*R*,4*S*,5*R*,6*R*)-3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-4-[(4′-bromobenzyl)oxy]-5-(phenylseleno)-2,7-dioxabicyclo[4.3.0]nonan-8-one (16a). To a solution of 5.12 g (10.28 mmol) of amide **8** in 55 mL of dry methylene chloride under N_2 at –78 °C was added 2.76 g of phenylselenenyl chloride. After 2 h at –78 °C, the pale yellow solution was allowed to warm to room temperature. A saturated aqueous solution of $NaHCO_3$ (70 mL) was added, and the resulting mixture was extracted with methylene chloride (2 × 70 mL). The combined methylene chloride fractions were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue over silica gel with methylene chloride and ethyl acetate–hexane (1:2) afforded 0.14 g (1.8%) of lactone **16c**, 5.50 g (85.5%) of lactone **16a**, and 0.23 g (4.4%) of lactone **16b**.

16c: R_f 0.51 (silica gel, methylene chloride); IR (thin film) 3034, 2928, 1775, 1477, 1253, 1183, 1101, 730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 3.63–3.73 (m, 3 H), 3.99–4.01 (m, 3 H), 4.10–4.69 (m, 4 H), 7.1–8.0 (m, 14 H); MS (70 eV) m/z 725 (M^+), 569, 537, 450, 169; HRMS calcd for $C_{29}H_{30}O_5{}^{80}Se_2Si^{79}Br$ 724.9376, found 724.9375.

16a: R_f 0.37 (silica gel, methylene chloride); IR (thin film) 2953, 1780, 1595, 1253, 1108, 1010, 837 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.03 (s, 3 H), 0.05 (s, 3 H), 2.58–2.68 (m, 2 H), 3.66–3.67 (m, 3 H), 3.84 (m, 1 H), 4.00 (s, 1 H), 4.30 (d, 1 H, J = 12.0 Hz), 4.44 (s, 1 H), 4.50–4.54 (m, 2 H), 7.09–7.50 (m, 9 H); MS (70 eV) m/z 569 (M^+ – t-Bu) 413, 383, 275, 245, 169; HRMS calcd for $C_{23}H_{26}O_5Si^{81}Br^{80}Se$ 570.9878, found 570.9878.

16b: R_f 0.53 (silica gel, 33% ethyl acetate–hexane); IR (thin film) 3370, 2900, 1790, 1620, 1160, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.90 (m, 1 H), 2.70 (s, 2 H), 3.50–3.61 (m, 2 H), 3.81–3.91 (m, 2 H), 4.04 (s, 1 H), 4.23 (s, 1 H, J = 12.02 Hz), 4.48 (s, 1 H), 4.56–4.60 (m, 2 H), 7.04–5.54 (m, 9 H); MS (70 eV) m/z 512 (M^+), 327, 295, 237, 169.

(1*S*,3*R*,4*R*,6*S*)-3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-4-[(4′-bromobenzyl)oxy]-2,7-dioxabicyclo-[4.3.0]nonan-8-one (17). A solution of the lactone **16a** (10.01 g, 16.0 mmol) in 100 mL of freshly distilled toluene was mixed with 7.30 mL (27.1 mmol) of tributylin hydride and 78 mg (0.48 mmol) of AIBN. The mixture was degassed with a stream of nitrogen for 15 min and heated to 110 °C for 1.5 h.

Removal of the solvent and flash chromatography of the residue over silica gel with hexanes–ethyl acetate (2:1 to 1:1) afforded 6.38 g (90%) of lactone **17** as an oil which crystallized on standing under vacuum: mp 105–106 °C (ether + hexanes); R_f 0.22 (silica gel, 33% ethyl acetate–hexane); IR (thin film) 2930, 1780, 1470, 1165, 839, 777 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.00 (s, 3 H), 0.03 (s, 3 H), 0.87 (s, 9 H), 1.74 (dt, J = 16.06, 3.82 Hz), 2.58–2.80 (m, 3 H), 3.47 (m, 1 H), 3.63–3.78 (m, 3 H), 4.31–4.42 (m, 3 H), 4.67 (d, 1 H, J = 11.82 Hz), 7.28 (d, 1 H, J = 8.53 Hz), 7.45 (d, 1 H, J = 8.35 Hz); MS (70 eV) m/z 415, 413 (M^+ – t-Bu), 313, 243, 229, 169; HRMS calcd for $C_{17}H_{22}O_5Si^{79}Br$ 413.0420, found 413.0420.

(1*S*,3*R*,4*R*,6*S*,8*R*)-4-[(4′-Bromobenzyl)oxy]-3-(hydroxymethyl)-8-(methyloxy)-2,7-dioxabicyclo[4.3.0]nonane (19). To a solution of 4.90 g (10.4 mmol) of lactone **17** in 260 mL of dry toluene cooled to –78 °C was added dropwise 40.0 mL of DIBAL (1 M solution in hexane). After 2 h at –78 °C, the reaction was cautiously quenched by the addition of 15 mL of methanol and 15 mL of saturated aqueous NH_4Cl. The reaction mixture was diluted with 250 mL of ether and warmed to room temperature. The gelatinous solution was filtered on a Celite pad, and the filtrate was washed with brine (2 × 100 mL). The combined aqueous fractions were backwashed with ether (100 mL). The combined ether fractions were dried over Na_2SO_4 and concentrated under reduced pressure to give 5.01 g of colorless oil. The residue was passed through a small plug of silica gel using 25% methylene chloride–ethyl acetate. The material obtained was used directly in the next reaction without further purification.

To a solution of the above lactol in 150 mL of methanol was added 0.38 g of p-TsOH. The mixture was stirred at room temperature until no starting material was present by TLC (usually 2 h). The methanol was removed by rotary evaporation, and the residue was diluted with 50 mL of saturated aqueous $NaHCO_3$ and extracted with ethyl acetate (3 × 100 mL). The combined extracts were dried (Na_2SO_4), concentrated, and chromatographed on silica gel (ethyl acetate) to give 2.40 g of the α-anomer and 0.49 g of β-anomer **19** (75%): R_f 0.55 [α-anomer], 0.30 [β-anomer] (silica gel, ethyl acetate); IR (thin film) 3456, 2883, 1468, 1363, 1093, 1026, 806 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.74 (ddd, 1 H, J = 15.83, 4.41, 4.29 Hz), 2.00 (m, 1 H), 2.09 (ddd, 1 H, J = 14.78, 5.40, 3.48 Hz), 2.40 (dd, 1 H, J = 14.78, 5.88 Hz), 2.57 (d, 1 H, J = 15.82 Hz), 3.30–3.61 (m, 3 H), 3.47 (s, 3 H), 3.86 (m, 1 H), 3.98 (m, 1 H), 4.11 (m, 1 H), 4.37 (d, 1 H, J = 12.40 Hz), 4.71 (d, 1 H, J = 12.40 Hz), 5.24 (dd, 1 H, J = 5.70, 3.52 Hz), 7.24 (d, 2 H, J = 8.30 Hz), 7.46 (d, 2 H, J = 8.30 Hz); MS (70 eV) m/z 371, 340 (M^+ – MeOH), 311, 265, 251, 237, 169; HRMS calcd for $C_{15}H_{17}O_4{}^{78}Br$ 340.0310, found 340.1309.

(1*S*,3*R*,4*R*,6*S*,8*R*)-4-[(4′-Bromobenzyl)oxy]-3-(cyanomethyl)-8-(methyloxy)-2,7-dioxabicyclo[4.3.0]nonane (20). To a solution of pyridine (0.69 mL, 8.54 mmol) and the above alcohol **19** (1.45 g, 3.88 mmol) in 90 mL of dry methylene chloride, cooled to –42 °C, was added dropwise a solution of triflic anhydride (1.18 mL, 6.98 mmol) in 10 mL of methylene chloride over 25 min. After stirring for 5 min, the powered sodium cyanide (0.95 g, 19.4 mmol) and 100 mL of HMPA were added to the resulting white reaction mixture. The solution was allowed to reach room tem-

perature, and stirring was continued for an additional 7 h, after which time the reaction mixture was diluted with 50 mL of methylene chloride and washed successively with 5% aqueous $NaHCO_3$ (3 × 50 mL), water (50 mL), and brine. After concentration of the dried (Na_2SO_4) organic phase in vacuo, the crude product was purified by flash chromatography on silica gel with 50% ethyl acetate–hexane as eluent to furnish 998 mg (68%) of nitrile **20** as a colorless oil: R_f 0.60 (silica gel, 50% ethyl acetate–hexane); IR (thin film) 2850, 2252, 1490, 1360, 1095, 1115, 805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (ddd, 1 H, J = 16.05, 4.32, 4.26 Hz), 2.04 (ddd, 1 H, J = 14.73, 5.49, 3.66 Hz), 2.36 (dd, 1 H, J = 14.73, 5.85 Hz), 2.55–2.75 (m, 3 H), 3.38 (s, 3 H), 3.49 (m, 1 H), 3.65 (td, 1 H, J = 7.05, 1.50 Hz), 3.97 (m, 1 H), 4.12 (m, 1 H), 4.36 (d, 1 H, J = 12.45 Hz), 4.70 (d, 1 H, J = 12.45 Hz), 7.25 (d, 2 H, J = 8.30 Hz), 7.47 (d, 2 H, J = 8.30 Hz); MS (70 eV) m/z 383, 381 (M^+), 349, 270, 185, 169; HRMS calcd for $C_{17}H_{26}O_4N^{81}Br$ 383.0555, found 383.0555.

(1*S*,3*R*,4*R*,6*S*,8*R*)-4-[(4′-Bromobenzyl)oxy]-8-(methyloxy)-3-(2-oxoethyl)-2,7-dioxabicyclo[4.3.0]nonane. To a solution of the nitrile **20** (2.25 g, 5.89 mmol) in 50 mL of dry methylene chloride cooled to −78 °C was added 7.65 mL (7.65 mmol) of DIBAL (1 M solution in hexane) under N_2. The reaction mixture was allowed to stir at this temperature for 2 h, and then the reaction mixture was cautiously quenched by the addition of 10 mL of methanol and 10 mL of a saturated solution of NH_4Cl. The above reaction mixture was diluted with 150 mL of ether and warmed to room temperature. The gelatinous solution was filtered on a Celite pad, and the ether solution was washed with brine (50 mL). The organic layer was dried with $MgSO_4$, and the solvent was removed under reduced pressure. Chromatography of the crude oil on silica gel (66% ethyl acetate–hexane) afforded 1.75 g (77%) of the aldehyde as a clear oil: R_f 0.46 (silica gel, 66% ethyl acetate–hexane); IR (thin film) 2860, 1710, 1480, 1100, 1030, 806 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.79 (m, 1 H), 2.05 (m, 1 H), 2.33 (dd, 1 H, J = 14.5, 5.7 Hz) 2.51–2.63 (m, 3 H), 2.81 (ddd, 1 H, J = 17.0, 7.1, 1.7 Hz), 3.35 (m, 1 H), 3.38 (s, 3 H), 3.85 (m, 1 H), 3.97 (m, 1 H), 4.11 (m, 1 H), 4.35 (d, 1 H, J = 12.2 Hz), 4.69 (d, 1 H, J = 12.2 Hz), 5.21 (m, 1 H), 7.23 (d, 2 H, J = 8.3 Hz), 7.46 (d, 1 H, J = 8.3 Hz), 9.30 (m, 1 H); MS (70 eV) m/z 354, 352 (M^+ – MeOH), 334, 279, 264, 185, 169; HRMS calcd for $C_{16}H_{17}O_4{}^{79}Br$ 352.0310, found 352.0310.

(1*S*,3*R*,4*R*,6*S*,8*R*)-4-[(4′-Bromobenzyl)oxy]-3-[2(*S*)-hydroxy-3(*E*)-pentenyl]-8-(methyloxy)-2,7-dioxabicyclo-[4.3.0]nonane (21). To a solution of 2.62 g (6.69 mmol) of CuI·Bu_3P in 150 mL of dry ether at −42 °C was added dropwise 23 mL of a 0.58 M ethereal solution of *trans*-1-propenyllithium. The resulting solution was allowed to stir at −42 °C for 30 min at which time 0.86 g (2.23 mmol) of the above aldehyde was added in 20 mL of ether. After stirring at −42 °C for 10 h, the solution was allowed to reach room temperature, and then the mixture was quenched with a 1:1 solution of 3% aqueous NH_4OH and saturated NH_4Cl. The layers were partitioned, and the aqueous phase was extracted with ether (2 × 60 mL). The combined ethereal layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (ethyl acetate) of the residue on a silical gel column gave 0.81 g (85.3%) of the allylic alcohol **21** as two diastereomers (ratio of 7.3:1 by isolation): R_f 0.51 (major), 0.30 (minor) (silica gel, ethyl acetate); IR (thin film) 3470, 2940, 1490, 1365, 1210, 1100, 1015, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (d, 3 H, J = 6.37 Hz), 1.76–1.80 (m, 1 H), 2.01–2.13 (m, 3 H), 2.35 (ddd, 1 H, J = 14.62, 5.53, 4.04 Hz), 2.57 (d, 1 H, J = 15.61 Hz), 2.85 (d, 1 H, J = 1.89 Hz), 3.24–3.28 (m, 1 H), 3.37 (s, 3 H), 3.46–3.52 (m, 1 H), 3.93–3.95 (m, 1 H), 4.06–4.11 (m, 1 H), 4.17–4.20 (m, 1 H), 4.40 (d, 1 H, J = 12.49 Hz), 5.22 (dd, 1 H, J = 5.77, 3.63 Hz); 5.45–5.70 (m, 2 H), 7.25 (d, 2 H, J = 8.0 Hz), 7.45 (d, 2 H, J = 8.0 Hz); MS (70 eV) m/z 396, 378, 376 (M^+ – H_2O – MeOH) 297, 279, 239, 209, 171; HRMS calcd for $C_{19}H_{21}O_3{}^{79}Br$ 376.0675, found 376.0674.

(1*S*,3*R*,4*R*,6*S*,8*R*)-4-Hydroxy-3[2(*S*)-hydroxy-3(*E*)-pentenyl]-8-(methyloxy)-2,7-dioxabicyclo[4.3.0]nonane (6). To a stirred solution of 1.35 g (3.16 mmol) of bromobenzyl ether **21a** and 0.124 g (3.16 mmol) of sodium amide in 20 mL of THF and 60 mL of liquid NH_3 (redistilled from lithium) at −78 °C under argon was added 22 mg (6.30 mmol) of lithium. Because the characteristic blue color appeared and decolorized immediately, an additional 44 mg (12.6 mmol) of lithium was added. After 30 min at −78 °C, the reaction was quenched by the careful addition of ammonium chloride, and then the NH_3 was allowed to evaporate under a stream of nitrogen. The resulting residue was diluted with saturated aqueous NH_4Cl and extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel with ethyl acetate afforded 759 mg (93.0%) of diol **6** as a colorless oil: R_f 0.42 (silica gel, ethyl acetate); IR (thin film) 3450, 2900, 1600, 1450, 1370, 1205, 1103, 1025, 860 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55–1.62 (m, 1 H), 1.69 (dd, 3 H, J = 5.72, 1.95 Hz), 1.88–2.05 (m, 3 H), 2.31–2.45 (m, 2 H), 2.93 (m, 2 H), 3.39 (s, 3 H), 3.51–3.60 (m, 2 H), 4.07–4.11 (m, 2 H), 4.29 (m, 1 H), 5.19 (dd, 1 H, J = 5.78, 3.76 Hz), 5.49–5.52 (m, 1 H), 5.67–5.71 (m, 1 H); MS (70 eV) m/z 226 (M^+ – MeOH), 208, 191, 180, 156, 127, 111; HRMS calcd for $C_{12}H_{18}O_4$ 226.1205, found 226.1204.

(1*R*,3*S*,5*R*,7*S*,9*R*,11*S*,12*S*)-11-Ethyl-12-hydroxy-5-(methyloxy)-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane (5). To a stirred solution of the olefinic alcohol **6** (385 mg, 1.49 mmol) in 20 mL of dry THF cooled to 0 °C under N_2 was added mercuric trifluoroacetate (3.18 g, 7.45 mmol). The reaction mixture was stirred at 0–5 °C for 6 h and then at 23 °C for 18 h in the dark. At this time, pyridine·HBr_3 (1.79 g, 4.47 mmol) in 5 mL of dry pyridine was added, and the reaction was stirred at 23 °C for 5 h. This mixture was then poured into a half-saturated aqueous solution of $Na_2S_2O_3$ (20 mL) and extracted with ether (3 × 50 mL), and the organic extracts washed with 2.5% aqueous NaOH (2 × 30 mL) and brine. The combined extracts were dried over Na_2SO_4 and concentrated to give a slightly yellow oil [R_f 0.56, 0.50 (silica gel, 33% methylene chloride–ethyl acetate)]. This crude bromide was dissolved in 15 mL of fleshly distilled toluene, and after the addition of tributyltin hydride (0.8 mL, 2.97 mmol) and AIBN (7 mg, 0.04 mmol), the resulting mixture was heated to 105 °C for 1.5 h under N_2. Evaporation of the solvent and chromatography of the residue over silica gel (33% methylene chloride–ethyl acetate) afforded 250 mg (65%) of the hydroxypyranopyran **5**: R_f 0.51 (silica gel, 25% methylene chloride–ethyl acetate); IR (thin film) 3530, 2930, 1450, 1150, 1030, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (t, 3 H, J = 7.53 Hz), 1.69 (q, 7.29), 1.76 (m, 1 H, J = 14.7, 3.35, 3.22 Hz), 1.95 (ddd, 1 H, J = 16.0, 4.95, 4.88 Hz), 2.06 (m, 1 H, J = 14.83, 5.48, 3.58 Hz), 2.22 (ddd, 1 H, J = 14.7, 2.76, 2.68 Hz), 2.26–2.41 (m, 3 H), 3.10–3.16 (m, 2 H), 3.38 (s, 3 H), 3.43–3.56 (m, 2 H), 3.55 (m, 1 H), 3.89 (m, 1 H), 5.18 (dd, 1 H, J = 5.58, 3.67 Hz); MS (70 eV) m/z 258 (M^+), 240, 226, 208, 185, 169, 151, 145, 127, 81, 71; HRMS calcd for $C_{13}H_{22}O_5$ 258.1467, found 254.1467.

(1*R*,3*S*,5*R*,7*S*,9*R*,11*S*,12*R*)-12-Bromo-5-(methyloxy)-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane (25a) and (1*R*,3*S*,5*R*,7*R*,9*R*,11*S*,12*R*)-12-Bromo-11-ethyl-5-hydroxy-2,6,10-trioxatricyclo[7.4.0.0^{3,7}]tridecane (25b). To a solution of **5** (66 mg, 0.255 mmol) in 6 mL of dry benzene cooled to 5 °C was added dropwise 23 μL (0.27 mmol) of freshly distilled thionyl bromide. After stirring for 45 min at this temperature, the mixture was poured into a saturated aqueous solution of $NaHCO_3$ and extracted with methylene chloride (3 × 20 mL). The organic extracts were combined, dried (Na_2SO_4), concentrated, and chromatographed (66% ethyl acetate–hexane) to afford 32 mg (40%) of **25a** and 20 mg (25%) of **25b**. **25a**: R_f 0.55 (silica gel, 33% methylene chloride–ethyl acetate); IR (thin film) 2918, 2849, 1462, 1404, 1140, 1088, 962, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 7.5 Hz), 1.62–1.69 (m, 2 H), 1.74–1.79 (m, 1 H), 1.87–1.93 (m, 1 H, J = 16.0 Hz), 2.20–2.21 (m, 1 H, J = 14.6 Hz), 2.46–2.51 (m, 1 H, J = 16.0 Hz), 3.12 (m, 1 H, J = 6.93, 6.75 Hz), 3.41 (s, 3 H), 3.47–3.51 (m, 3 H), 3.86 (m, 1 H, J = 12.5 Hz), 4.01 (m, 1 H), 4.17 (m, 1 H), 4.42 (m, 1 H), 5.12 (m, 1 H); MS (70 eV) m/z 320, 318, 288, 286, 239, 225, 207, 107, 81.

25b: R_f 0.33 (silica gel, 33% methylene chloride–ethyl acetate); ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7.5 Hz), 1.57–1.69 (m, 2 H), 1.82–1.98 (m, 2 H), 2.23–2.29 (m, 1 H, J = 15.2 Hz), 2.58 (m, 1 H, J = 15.8 Hz), 2.65 (m, 1 H, J = 8.6 Hz), 3.20 (m, 1 H), 3.55 (m, 2 H), 3.62 (m, 1 H), 4.22 (m, 2 H), 4.42 (m, 1 H), 4.66 (d, 1 H, J = 9.13 Hz), 5.47 (d, 1 H, J = 9.18 Hz).

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Supplementary Material Available: Structural report for the organomercurial **23b**, including a description of data collection, atomic coordinates, isotropic thermal parameters, bond lengths, bond angles, and anisotropic thermal parameters, and 300-MHz ^{1}H NMR spectra of **5**, **6**, **8**, **17**, **19-21**, **25a**, and **25b** (20 pages). Ordering information is given on any current masthead page.

Syntheses and Reactions of Silyl Carbamates. 1. Chemoselective Transformation of Amino Protecting Groups via *tert*-Butyldimethylsilyl Carbamates

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The *N*-*tert*-butyldimethylsilyloxycarbonyl group (silyl carbamate) was synthesized from commonly used amino protecting groups such as *N*-*tert*-butoxycarbonyl (Boc) and *N*-benzyloxycarbonyl (Z) by treatment with *tert*-butyldimethylsilyl trifluoromethanesulfonate/2,6-lutidine and *tert*-butyldimethylsilane/$Pd(OAc)_2$, respectively. This novel species, upon activation with fluoride ion, reacts with a variety of electrophiles to give *N*-ester type compounds in high yield. For example, the conversion of *N*-*t*-Boc compounds into their corresponding *N*-Z compounds via a silyl carbamate was accomplished under these mild reaction conditions.

The *N*-trialkylsilyloxycarbonyl group (silyl carbamate) is a species which was first prepared by Breederveld in 1962 by means of insertion of carbon dioxide into an *N*-trialkylsilyl compound (eq 1).[1] This group can be viewed as a masked form of an *N*-carboxylate ion, an extremely unstable species observed during removal of urethane type amino protecting groups under strongly acidic conditions.[2] However, the silyloxycarbonyl species has received little attention from chemists in spite of its considerable synthetic potential. The only other example of the synthesis of a silyl carbamate reported to date is the introduction of this group into partial structures of drugs in order to improve their efficiencies; the preparation in this case involved condensation of trialkylsilanol with an isocyanate (eq 2).[3] No further reports concerning either its reactivity or synthetic potential have appeared since.

$$RNHSiR'_3 + CO_2 \rightarrow RNHCO_2SiR'_3 \quad (1)$$

$$RNCO + R'_3SiOH \rightarrow RNHCO_2SiR'_3 \quad (2)$$

We believed that an *N*-silyloxycarbonyl compound activated by fluoride ion would react with an electrophile to give the corresponding *N*-ester type compound. Our attention was focused on the synthesis of a silyl carbamate from commonly used urethane type amino protecting groups such as *N*-*tert*-butoxycarbonyl (*t*-Boc) and *N*-benzyloxycarbonyl (Z), both representative amino protecting groups used for amino acids, amino sugars, peptides, and alkaloids.[4] We detail below new methods for the synthesis of *tert*-butyldimethylsilyl carbamate from *N*-Z and *N*-*t*-Boc groups and its conversion into amines and various *N*-ester type compounds (eq 3) (i.e., *N*-*t*-Boc group into *N*-Z group via silyl carbamate).[5]

$$RNHCO_2R^1 \longrightarrow [RNHCO_2^-] \longrightarrow RNHCO_2SiR^2_3 \xrightarrow{R^3X} RNHCO_2R^3 \quad (3)$$
$$\downarrow$$
$$RNH_2$$

Results and Discussion

Synthesis of *tert*-Butyldimethylsilyl Carbamate from the *N*-*tert*-Butoxycarbonyl (*t*-Boc) Group. The *N*-*t*-Boc group is stable to a variety of chemical transformations, especially under basic conditions, due to its sterically bulky nature, but is easily removed under acidic conditions.[4] Recently, several groups have reported efficient methods for the deprotection of the *N*-*t*-Boc group by the use of trimethylsilyl perchlorate (Me_3SiClO_4),[6] trimethylsilyl iodide (Me_3SiI),[7] and trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf).[8] Since these methods were used only for removal of the *t*-Boc group under strongly acidic conditions, the putative *N*-$CO_2Si(CH_3)_3$ intermediate could not be detected (eq 4).

$$RNHCO_2\text{-}t\text{-}Bu \xrightarrow{Me_3SiX} [RNHCO_2SiMe_3] \rightarrow RNH_2HX \quad (4)$$
$$X = I, OTf, ClO_4$$

During the course of our studies on the synthesis of biologically active peptides,[9] we found that *tert*-butyldimethylsilyl trifluoromethanesulfonate (*t*-$BuMe_2SiOTf$), a powerful silylating reagent of a hydroxyl group,[10] in the presence of 2,6-lutidine can be used to effect the transformation of the *t*-Boc group into the *N*-*tert*-butyldimethylsilyloxycarbonyl group (**1a**-**2a**). The ^{1}H NMR ($CDCl_3$) data of **2a** [δ 0.90 (s, 9 H), 0.84 (s, 9 H), 0.25 (s,

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