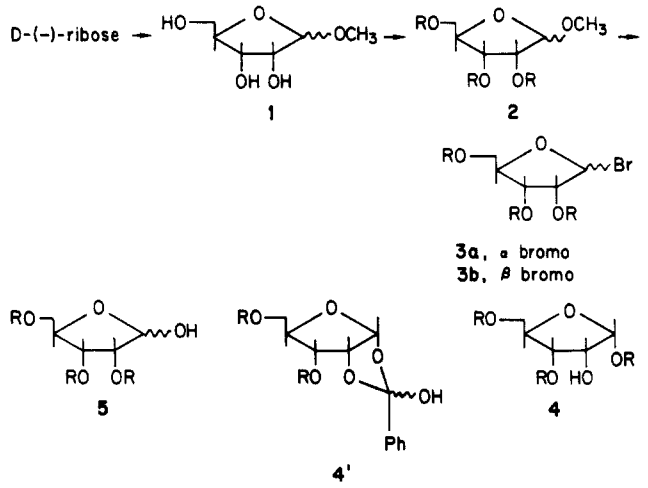
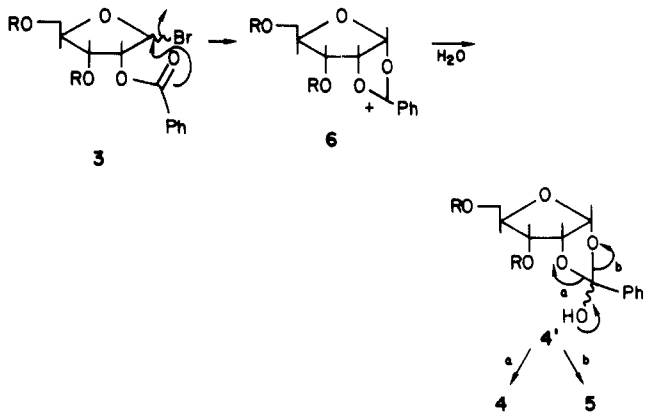
Scheme I[a]



[a] R = COPh.

Scheme II

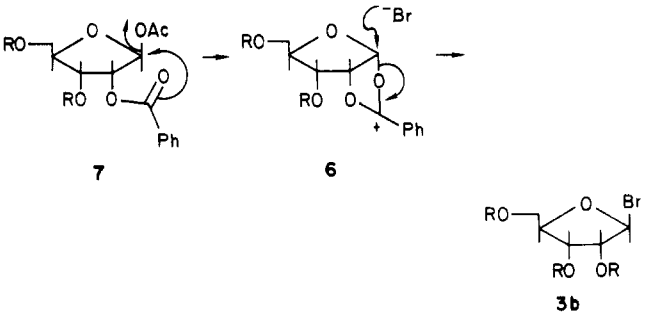


large excess HBr. When we carried out the reaction with 1.1 equiv of HBr in CH_2Cl_2 at 0 °C, the pure β-anomer **3b** was obtained. Using a 0.5 molar solution of HBr in CH_2Cl_2, only the β-bromo anomer was observed to form with 2, 4, or 10 equiv of HBr. However, as reported, a mixture of bromo anomers was obtained when HBr was bubbled directly into a CH_2Cl_2 solution of 8 at 0 °C.

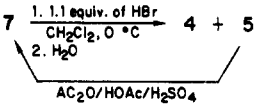
Thus the bromination of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (**7**) with 1.1 equiv of HBr in CH_2Cl_2 at 0 °C resulted in a smooth conversion to the β-anomer **3b** as shown in Scheme III. After 1 h, when the bromination was complete, water was added and the two phases were vigorously stirred. Both the bromination and solvolysis were monitored for completion by observing the respective anomeric protons in the NMR spectrum. The crystalline product **4** was obtained in 63% yield by addition of heptane to the dried CH_2Cl_2 solution.[5] The filtrate resulting from the removal of **4** was shown by NMR to contain the mixture of anomers **5**. After removal of the solvent, **5** was recycled to **7** by treatment with acetic anhydride, acetic acid, and sulfuric acid[6] in 78% yield.

The process described in Scheme IV gives an 81% yield of 1,3,5-tri-*O*-benzoyl-α-D-ribofuranose (**4**) with a single recycle of **5**. The material prepared in this manner has been used to prepare 2-substituted sugars and the corresponding nucleosides which will be the subject of a companion paper.[7]

Scheme III



Scheme IV



Registry No. **3b**, 16205-60-0; **4**, 22224-41-5; **5** (α-anomer), 79439-67-1; **5** (β-anomer), 67525-66-0; **8**, 6974-32-9.

(5) This reaction was successfully carried out on a 1.8-mol scale in 50–60% yield by D. G. Mikolasek and L. A. Reif of Chemical Process Development, Bristol-Myers Pharmaceutical Research and Development, Evansville, IN.

(6) Recondo, E. F.; Rinderknecht, H. *Helv. Chim. Acta* **1959**, *42* (121), 117.

(7) Tann, C. H.; Brodfuehrer, P. R.; Brundidge, S. P.; Sapino, C.; Howell, H. G. *J. Org. Chem.*, in press.

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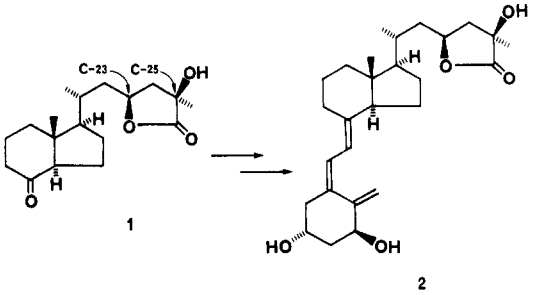
A Highly Stereoselective Route to Calcitriol Lactone[1]

Summary: Keto lactone **1**, the key intermediate for producing the title substance **2**, has been synthesized from the known diol **3** by a highly stereoselective scheme involving chiral acetal methodology (**7** + **8** → **9**) for producing the C-23 center (23*S*:23*R* = 98.5:1.5) and Bartlett iodocyclization methodology (**12** → **13**) followed by hydrolytic inversion (**14** → **15**) for generating the C-25 chiral center (25*R*:25*S* = 93:7).

Sir: The lactone **1**, having six chiral centers, is the key intermediate for the impressive Hoffmann-La Roche–U.C. Riverside synthesis[2] of calcitriol lactone (**2**), a major metabolite of vitamin D_3. This synthesis of **1** suffered only



(1) This paper represents paper 11 in the series "Asymmetric Synthesis via Acetal Templates". For paper 10, see: Johnson, W. S.; Edington, C.; Elliott, J. D.; Silverman, I. R. *J. Am. Chem. Soc.* **1984**, *106*, 7588–7591.

(2) Wovkulich, P. M.; Baggiolini, E. G.; Hennessy, B. M.; Uskokovic, M. R.; Mayer, E.; Norman, A. W. *J. Org. Chem.* **1983**, *48*, 4433–4436.

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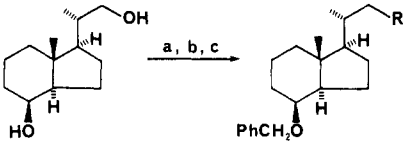
with respect to the stereoselectivity of the processes used to generate the side-chain chiral centers at C-23 and C-25, each of which involved the separation of 1:1 diastereomeric mixtures. The present communication discloses a conceptually different approach to **1** which is highly stereoselective throughout, the aforementioned chiral centers being generated in selectivities of 98.5:1.5 and 93:7, respectively.

The strategy for realizing stereoselective production of the chiral center at C-23 involved use of our chiral acetal methodology,[3] i.e., the coupling of the acetal **7** with the methallylsilane **8** to give **9**. The development of the C-25 chiral center, in turn, envisaged application of the Bartlett iodocyclization methodology[4] (**12** → **13**) followed by a hydrolytic stereochemical inversion (**14** → **15**) according to a procedure of Nakanishi et al.[5] The results of exploiting this plan are set forth below.

The Inhoffen–Lythgoe diol **3**, which is available by highly stereoselective total asymmetric synthesis[9] as well as via degradation (O_3, $NaBH_4$) of vitamin D_2,[10] was chosen as the starting material. Its conversion, via the tosylate

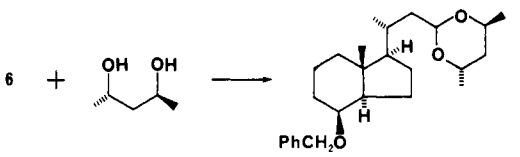


3 **4** R = OH; **5** R = CN; **6** R = CHO

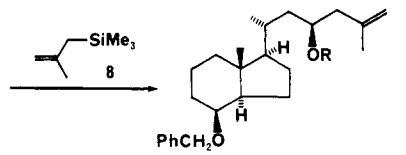
[a] To give **4**: selective *tert*-butyldimethylsilylation[6] of primary OH; 5 molar equiv of NaH, DMF, then 3 molar equiv of $PhCH_2Br$, 18 h, 23 °C; 2 molar equiv of *n*-Bu_4NF, THF, 4 h, 23 °C. [b] To give **5**: 1.6 molar equiv of TsCl, C_5H_5N, 3 h, 23 °C; 8 molar equiv of KCN, DMF, 20 h, 55–60 °C. [c] To give **6**: 2 molar equiv of DIBAH (toluene), CH_2Cl_2, 30 min, 0 °C

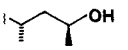
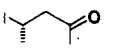
of **4**[7,8] and the nitrile **5**,[7,8] into the aldehyde **6**,[7,8a,b] was unexceptional. Reaction of **6** with (*S,S*)-2,4-pentanediol (1.2 molar equiv of diol, 0.01 M $C_5H_5NH{\cdot}OTs$ in C_6H_6, 3-h reflux) afforded acetal **7**[7,8] (54% overall yield from **3**).

The coupling of acetal **7** with methallyltrimethylsilane (**8**) was performed according to a previously described procedure[11] using $6TiCl_4{\cdot}5Ti(O\text{-}i\text{-}Pr)_4$ as the catalyst. The product **9**[7,8a,b] (94% yield) was obtained in 98.5:1.5 (23*S*:23*R*) diastereomeric ratio.[12a] Removal of the chiral auxiliary was achieved,[11] in 95% overall yield, by PCC



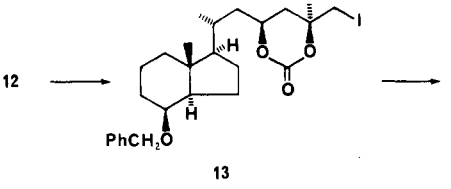
7



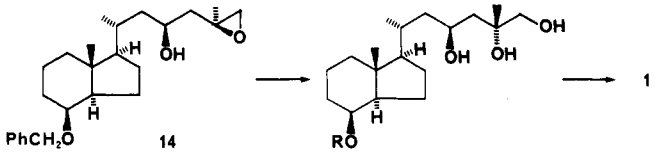
9 R =  **10** R = 

11 R = H
12 R = CO_2t-Bu

oxidation to give the ketone **10**,[7,8] followed by β-elimination, affording **11**.[7,8a,b] The Bartlett procedure[4] was used to convert the homoallylic alcohol **11** into the corresponding *tert*-butyl carbonate **12**[7,8] (94% yield), which was then subjected to iodocyclization[4] (3 molar equiv of I_2, CH_3CH_2CN, −40 °C, 30 min), affording the iodo carbonate **13**[7,8] (mp 109–110 °C) in 85% yield and >50:1 diastereomeric selectivity.[12b] Higher reaction temperatures and/or longer reaction times gave poorer selectivity, and the fact that the 50:1 selectivity is a result of kinetic control was demonstrated by "equilibrating" the reaction mixture (−10 °C, 14 h) to give a 5:1 mixture of diastereoisomers.[13]



13



14 **15** R = CH_2Ph; **16** R = H

Alkali treatment[4] (2.5 N KOH, H_2O/DME, 3 h, 20 °C) of **13** effected conversion into the epoxy alcohol **14**.[7,8] Hydrolysis of **14** under Nakanishi's conditions[5] (1:1 0.1 N H_2SO_4/THF, 2.5 h, 20 °C) yielded (92%) the triol **15**[7,8a,b] which proved to be a 94.3:5.7 mixture of 25*R*:25*S* diastereomers.[12c] Hydrogenolysis (10% Pd–C, 3 atm, H_2, MeOH, 7 h, 23 °C) of **15** furnished the crystalline tetrol **16** in 94%

(3) Johnson, W. S.; Crackett, P. H.; Elliott, J. D.; Jagodzinski, J. J.; Lindell, S. D. *Tetrahedron Lett.* **1984**, *25*, 3951–3954.
(4) Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829–4830. Bartlett, P. A.; Meadows, J. D.; Brown, E. G.; Morimoto, A.; Jernstedt, K. K. *J. Org. Chem.* **1982**, *47*, 4013–4018. See also: Bongini, A.; Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *Ibid.* **1982**, *47*, 4626–4633. Cardillo, G.; Orena, M.; Porzi, G.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1981**, 465–466.
(5) Nakanishi, K.; Schooley, D. A.; Koreeda, M.; Dillon, J. *J. Chem. Soc., Chem. Commun.* **1971**, 1235–1236. See also: Hanson, R. M. *Tetrahedron Lett.* **1984**, *25*, 3783–3786.
(6) Chaudhary, C. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99–102.
(7) The product was submitted to flash chromatography using Merck silica gel grade 60, 230–400 mesh.
(8) (a) The GC and TLC showed no indication of extraneous components. (b) The ^1H NMR and IR spectra were entirely consistent with the assigned structure. (c) A satisfactory combustion analysis was obtained for an appropriately purified specimen.
(9) (a) Trost, B. M.; Bernstein, P. R.; Funfschilling, P. C. *J. Am. Chem. Soc.* **1979**, *101*, 4378–4380. (b) Johnson, W. S.; Elliott, J. D.; Hanson, G. J. *Ibid.* **1984**, *106*, 1138–1139.
(10) Inhoffen, H. H.; Quinkert, G.; Schutz, S.; Friedrich, G.; Tober, E. *Chem. Ber.* **1958**, *91*, 781–791. We have developed a modification (O_3, 4:1 CH_2Cl_2/MeOH, −78 °C followed by excess $NaBH_4$ −78 to 0 °C) which gave **3** in 70% yield.
(11) Footnote 3 of ref 3.
(12) The diastereomeric ratios were determined by the following analytical techniques which showed base-line separation of the peaks for the epimers: (a) for product **9**, GC on a 15-m SE-54 capillary column at 240 °C; (b) for product **13**, HPLC on a (normal phase) DuPont Zorbax silica gel column, 20% EtOAc in hexane; (c) for product **15**, HPLC on a (reverse phase) DuPont Zorbax O.D.S. column, 15% H_2O in CH_3OH.
(13) The extraordinarily high stereoselectivity observed in this case is associated with the fact that the kinetic product can be isolated, a fact which appears to be associated with the presence of the tertiary O–C center β to the iodine atom. Thus iodocyclization of a model homoallylic system, unsubstituted on the olefinic bond, was a much slower process, and the composition of the initial product mixture (8:1), which may already have been equilibrated (cf. ref 4), was unaltered by prolonged treatment under the reaction conditions.

yield. Recrystallization from $MeOH/CH_2Cl_2$ gave, in 81% yield, diastereomerically pure material, mp 178–180 °C[7,8] (see below). Catalytic dehydrogenation[14] of **16** (Pt, O_2, 1:1 diglyme/H_2O, 20 h, 55 °C) in the presence of a trace of sodium lauryl sulfate,[15] quite remarkably, gave the lactone **1** in quantitative yield after flash chromatography.[7] This product was identical (NMR, IR, MS, TLC, GC coinjection, HPLC) with authentic **1**,[2,16] and there was no evidence for even a trace of the C-25 epimer, easily detectable by GC coinjection (base-line separation) as shown with authentic 25-*epi*-**1**.[16]

Thus we have achieved the synthesis of pure **1** in 28% overall yield from the Inhoffen–Lythgoe diol **3**. It is particularly noteworthy that this approach is so highly stereoselective that no separation of diastereomers is required; indeed, the trace contaminants of unnatural epimers are simply eliminated by a single recrystallization of the tetrol **16**.

Acknowledgment. We are indebted to the National Institutes of Health, the National Science Foundation and Pfizer, Inc. for grants in support of this research, and to Dr. John D. Elliott for helpful discussions. We also thank Professor Henry Rapoport[15] and Dr. Peter W. Wovkulich[16] for their assistance.

(14) Heyns, K.; Paulsen, H. In "Newer Methods of Preparative Organic Chemistry"; Foerst, W., Ed.; Academic Press: New York, 1963; Vol. 2, pp 303–305.

(15) Professor H. Rapoport suggested these reaction conditions. In the absence of the surfactant the reaction proceeded sluggishly, due to the insolubility of **16**, affording **1** in ca. 50% yield after 40 h at 55 °C.

(16) Dr. Peter M. Wovkulich of Hoffmann-La Roche, Inc. kindly provided us with samples of 8α-hydroxy lactone (**1** with an α-OH in place of the C=O at C-8) and its C-25 epimer, which we oxidized to authentic **1** and 25-*epi*-**1** by their procedure.[2]

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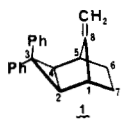
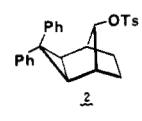
8-Methylene-*exo*-3,3-diphenyltricyclo[3.2.1.0^{2,4}]octane, a Probe for Addition Reaction Mechanism

Summary: The use of the title compound **1** as a mechanistic probe for addition reaction mechanism is suggested, based upon the pronounced proclivity of **1** to undergo quantitative and spectroscopically diagnostic rearrangement in ionic, but not nonpolar, additions.

Sir: Additions to the double bond in hydrocarbon **1** present interesting opportunities to explore the gererality of LRAMERO[1]-type rearrangements, which heretofore have been confined to solvolyses of secondary substrates such as **2**.[2]



1



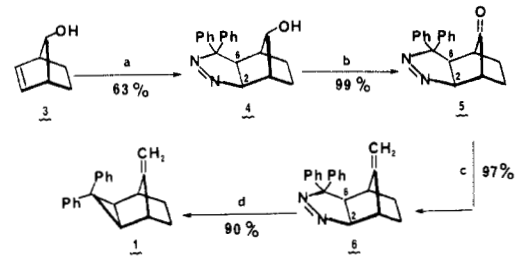
2

To investigate its potential for such rearrangement, **1** was synthesized as shown in Scheme I.

(1) Long-Range Aryl Migration coupled with Electrocyclic Ring Opening.

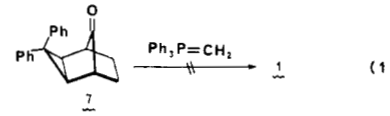
(2) For the latest paper in a series concerned with such electrocyclic effects in solvolysis, cf.: Wilt, J. W.; Curtis, V. A.; Congson, L. N.; Palmer, R. *J. Org. Chem.* **1984**, *49*, 2937.

Scheme I



[a] (a) Ph_2CN_2, 25 °C, 49 days; (b) PCC, CH_2Cl_2; (c) $Ph_3P{=}CH_2$, THF/hexane; (d) 165 °C.

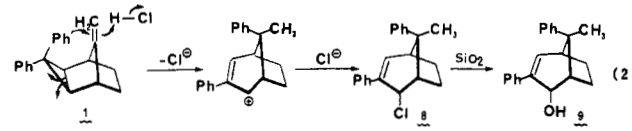
Addition of diphenyldiazomethane to *anti*-7-norbornenol (**3**) was best achieved by a "leave-it-alone" technique using the reactants with no solvent at room temperature.[3] Oxidation of the thus-formed exo[4] pyrazoline **4**, mp 158–158.5 °C dec ($C_{20}H_{20}ON_2$: calcd C, 78.90; H, 6.64. Found: C, 79.08; H, 6.70), with pyridinium chlorochromate easily afforded exo[4] ketone **5**, mp 154.5–155.5 °C, ν_{CO} 1770 cm^{-1} ($C_{20}H_{18}ON_2$: calcd C, 79.43; H, 6.01. Found: C, 79.22; H, 5.97), which underwent Wittig methylenation to produce exo[4] pyrazoline **6**, mp 163.5–164 °C, δ ($CDCl_3$) 4.1, 4.6; ν(KBr) 910 cm^{-1}, exocyclic $=CH_2$ ($C_{21}H_{20}N_2$: calcd C, 83.95; H, 6.72. Found: C, 83.65; H, 6.72). Finally, heating **6** led to waxy, crystalline hydrocarbon **1**, mp 72.5–73.5 °C, ^1H NMR δ ($CDCl_3$) 7.15, 3.70, 2.65, 1.65,[5] 1.50, all s, ratio 5:1:1:1:2, ν(KBr) 880 cm^{-1} ($=CH_2$), ^{13}C NMR δ ($CDCl_3$) 151.4, 147.1, 140.2, 130.7, 127.9, 127.4, 127.2, 125.6, 125.3, 99.7, 40.9, 36.7, 31.5, 28.7 ($C_{21}H_{20}$: calcd C, 92.58; H, 7.42. Found: C, 92.77; H, 7.36). Some points of interest attended the synthesis of **1**. All attempts to convert the known ketone **7**[6] to **1** by the Wittig reaction failed (eq 1).



(1)

Ketone **7** is clearly very hindered. Even methylmagnesium bromide failed to react with it, although methyllithium did so.[7]

The addition chemistry of **1** is under active investigation. But some early results testify to the utility of **1** as a probe substance. Ionic additions thus far investigated show that **1** indeed undergoes LRAMERO rearrangement readily. For example, addition of hydrogen chloride in CCl_4 led to **8** exclusively, as a 30:70 exo/endo mixture (eq 2). Chro-



(2)

matography converted the mixture to essentially pure *endo*-**8** and thence to alcohol **9** quantitatively, mp 116–117.5 °C ($C_{21}H_{22}O$: calcd C, 86.84; H, 7.65. Found: C, 86.68; H, 7.64). Definitive structural confirmation for *endo*-**8** and **9** rested upon the vinyl proton resonance, a

(3) Higher temperatures produced considerable benzophenone azine and the benzhydryl ether of **4** (mp 118.5–122 °C).

(4) This is the expected isomer, and the structure was confirmed by the clean doublet resonance ($J_{2,6}$ = 8 Hz) of H-2 at δ 4.9 (**4**), 5.1 (**5**), and 5.05 (**6**). Endo analogues exhibit a multiplet for H-2, caused by additional coupling to H-1.

(5) The singlet nature of this resonance for H-2,4 is characteristic of the exo tricycle, in contrast to the endo analogue. Cf. Wilt, J. W.; Sullivan, D. R. *J. Org. Chem.* **1975**, *40*, 1036.

(6) Wilt, J. W.; Malloy, T. P.; Mookerjee, P. K.; Sullivan, D. R. *J. Org. Chem.* **1974**, *39*, 1327.

(7) Mostly syn alcohol resulted (anti addition).

0022-3263/85/1950-2600$01.50/0