the solvent cage of the geminate dimolybdenum-alkyl radical pair formed upon homolysis of one of the Mo–C (alkyl) bonds. Further studies aimed at extracting mechanistic information are planned.[20]

Supplementary Material Available: Fractional coordinates and isotropic thermal parameters (3 pages). Ordering information is given on any current masthead page.

(20) We thank the Office of Naval Research and the Petroleum Research Fund, administered by the American Chemical Society, for support.

Stereoselective Synthesis of the Chiral Sequence of Erythronolide A

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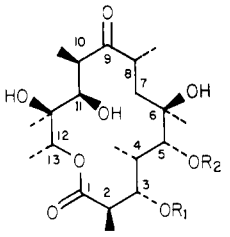
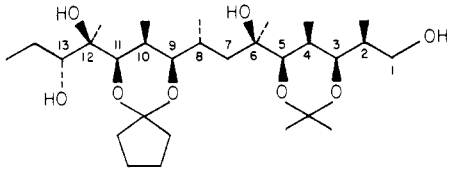
The sequence of ten chiral centers present in the aglycone derived from the well-known antibiotic erythromycin A (**1**)



1, R_1 = L-cladinose; R_2 = D-desosamine
2, $R_1 = R_2 = H$

presents a far from trivial synthetic challenge. The synthesis of the aglycone erythronolide A (**2**) has been achieved already by two Harvard groups,[1,2] one of which actually succeeded in putting together erythromycin A[2] itself.

We describe here a considerably simpler stereoselective synthesis of the protected polyol **3** in which all ten asymmetric centers of



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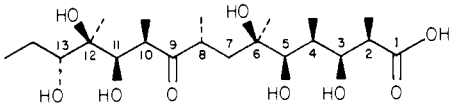

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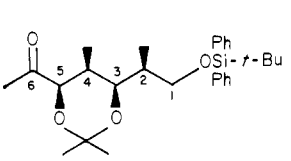
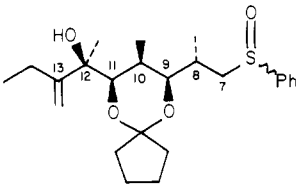
the seco acid **4** from erythronolide A are present in the correct absolute configuration.

The synthetic path we chose takes advantage of the fact that a cut of the molecule **3** and C_6 and C_7 as well as between carbons 12 and 13 produces two structurally and chirally identical fragments with the exception that C_2 and C_8 are antipodal. It is then possible to consider a construction in which chemically similar steps might be used to produce the two required fragments. These might also come from the same starting material. We now report the realization of this scheme in which the common chiral starting material for the two fragments **5** and **6** was chosen to be

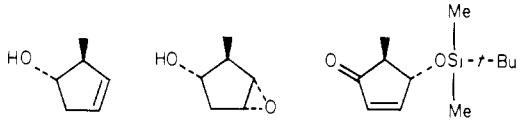


5



6

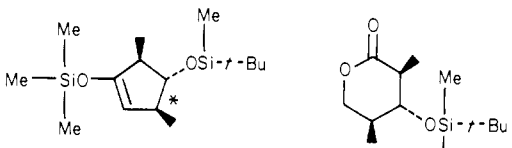
(1*S*,2*S*)-(+)-2-methyl-3-cyclopenten-1-ol (**7**), which is readily available from cyclopentadiene by the method of Partridge.[3] The cyclopentenol **7** was now transformed to the siloxycyclopentenone **9** by the sequence we had previously evolved[4] in connection with one of our prostaglandin syntheses.



7 **8** **9**

Hydroxyl-directed epoxidation of **7** with $VO(acac)_2$ and *tert*-butyl hydroperoxide in benzene[5] gave a single[6] epoxide, **8**[7] (86%), which, upon Jones oxidation, (0 °C, 25 min), followed by kinetically controlled β elimination of the epoxide (triethylamine in methylene chloride, 0.5 h) and in situ silylation of the liberated hydroxyl group (*t*-$BuMe_2SiCl$, DMAP) gave the (–)-enone **9** (83% from **8**).[8] The bulky siloxy group was expected to[9] —and did—control the approach of lithiodimethylcuprate to enone **9**: addition (ether, –78 °C), followed by trapping of the resulting enolate (Me_3SiCl, Et_3N) gave the single enol ether **10** (88%, purified[10]) in which the chiral centers have been correctly introduced to become the centers at C_2, C_3, and C_4 of the "right-hand fragment" **5**.

Further elaboration of **10** now required controlled introduction



10 **11**

of the center at C_5, as well as the necessary minor structural

†SRC/NATO Postdoctoral Research Fellow 1979–1980. Present address: Department of Chemistry, University College, London.

(1) Corey, E. J.; Hopkins, P. B.; Kim, S.; Yoo, S.; Nambiar, K. P.; Falck, J. R. *J. Am. Chem. Soc.* **1979**, *101*, 7131.

(2) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K. Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan-Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Soc.* **1981**, *103*, 3210, 3213, 3215. For another, very imaginative, approach to erythronolide which derives chirality from carbohydrate precursors, see: Hanessian, S.; Rancourt, G.; Guindon, Y. *Can. J. Chem.* **1978**, *56*, 1843.

(3) Partridge, J. J.; Chadha, N. K.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1973**, *95*, 532. The alcohol that was obtained in 50% yield via hydroboration of 5-methylcyclopentadiene with (–)-diisocampheylborane (from (+)-α-pinene and BH_3/THF) had $[\alpha]^{25}_D$ +170° (>95% ee).

(4) Stork, G.; Kowalski, C.; Garcia, G. *J. Am. Chem. Soc.* **1975**, *97*, 3258.

(5) Cf. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

(6) All purifications were done by flash chromatography (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(7) The epoxide **8** (ether elution) had a boiling point of 32–35 °C (0.2 torr); R_f 0.55 (ether); $[\alpha]^{25}_D$ +45.6° (*c* 1.02, MeOH).

(8) Enone **9** (methylene chloride elution) $[\alpha]^{25}_D$ –58.2° (*c* .78, MeOH); MS found 226.139; IR 1720 cm^{-1}; NMR δ 5.90 (1 H d) 7.08 (1 H dd).

(9) This type of stereocontrol has been well established in related cyclopentenone intermediates in prostaglandin synthesis; cf.: Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260.

(10) Enol silyl ether **10** (CH_2Cl_2 elution): R_f 0.8 (CH_2Cl_2); $[\alpha]^{25}_D$ +10.6° (*c* 1.2, $CHCl_3$); MS found 314.2099.

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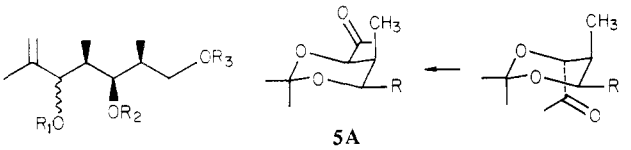
changes implicit in structure **5**. This was initiated by making the δ-lactone **11** (ozone, −78 °C, CH_2Cl_2; addition of methanol and sodium borohydride; acid-catalyzed cyclization (2 N HCl; 70% overall from **10**)).[11] Reduction (Dibal in THF, −78 °C) to the lactol and reaction with lithium 2-propenyl[12] in ether gave the diastereomeric mixture of adducts **12** (88%). The mixture was

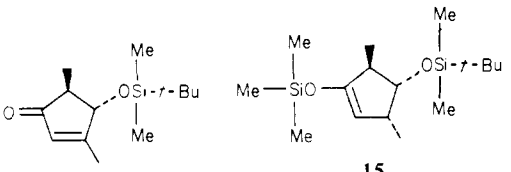


5A

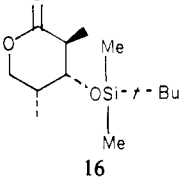
12, $R_1 = R_3 = H$; $R_2 = SiMe_2$-*t*-Bu
13, $R_1 = R_2 = CMe_2$; $R_3 = SiPh_2$-*t*-Bu

transformed to the acetonides **13** (91%) by a three-step sequence of desilylation (tetrabutylammonium fluoride in THF), selective silylation of the primary alcohol (t-$BuPh_2SiCl$/DMAP, CH_2Cl_2/Et_3N)[13] and acetonide formation ($(MeO)_2CMe_2$, catalytic pyridinium tosylate). Ozonolysis of **13** now gave the epimeric mixture of methyl ketones corresponding to structure **5**. The temporary lack of stereochemical control at C_5 is inconsequential because that center can now be established stereospecifically by "ancillary stereocontrol": the ancillary control element here is the *gem*-dimethyl group of the 1,3-dioxane system (cf. **5A**), which must result in a thermodynamic advantage of more than 3 kcal in favor of the equatorial acetyl group. Indeed, treatment of the mixture of methyl ketones with potassium carbonate in methanol (4 h) gave **5**[14] as the sole product (92% from **13**). This completes the stereospecific synthesis of the "right hand fragment" **5**, in proper chiral form.

The enol silyl ether **10**, which served as the C_2–C_4 chiral sequence of **5**, must now be inverted at the starred center so as to become the precursor of chiral sequence C_8–C_{10} of 6: oxidation of **10** to cyclopentenone **14** (Pd(II) acetate in acetonitrile[15]) was

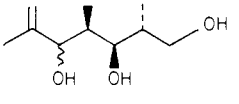


14 **15**

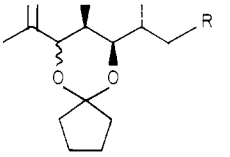


16

followed by hydrogenation 10% Pd–C in *tert*-butyl alcohol and silylation of the kinetic enolates of the resulting cyclopentanones[16] (LDA/THF, −78 °C, then Me_3SiCl). The mixture of silyl ethers **15** (major) and **10** thus obtained (87% from **10**) was ozonized and further transformed exactly as before (cf. **10** to **11**) to give the easily separated lactones **11** (the previously mentioned precursor of **5**) and **16**.[17] Lactone **16** was converted, as had been done with its epimer **11** to the triol mixture **17** (94%), which gave



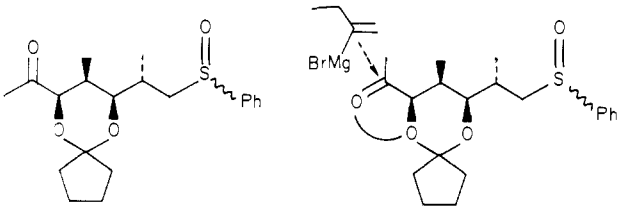
17



18, R = OTs
19, R = PhSO

the cyclopentylidene[18] ketal tosylate **18** ((a) TsCl, DMAP; Et_3N in CH_2Cl_2; (b) 1,1-dimethoxycyclopentane, catalytic pyridinium tosylate in CH_2Cl_2).

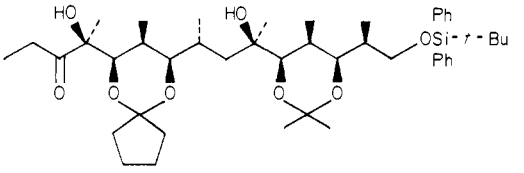
Establishment of the correct chirality at C_{11} now required keto sulfoxide **20**. This was simply prepared from sulfoxide **19** (sodium



20

thiophenoxide in ethanol, followed by sodium periodate in aqueous methanol; 76% from **17**) by ozonolysis and base equilibration, exactly as in the synthesis of **5**. The "left-hand fragment" **6** was now completed by addition of the Grignard reagent from 2-bromobutene (THF, −78 °C, 88%): coordination[18] of the entering organometallic reagent with the ketal oxygen was expected to (and did) produce the required chirality at C_{12}.

We were now ready to connect the left- and right-hand fragments. Coupling[19] of the dianion from **6** (2 equiv of LDA in glyme, −78 °C, 1 h) with methyl ketone **5** gave (80% yield at 50% conversion) a mixture that was separated into a major (more polar) and a minor isomer at C_6 (5:1).[20] Ozonolysis (CH_2Cl_2/CH_3OH; Me_2S) and desulfurization (W 2 Raney nickel in acetone, 1.5 h) of the major isomer now gave the ketol **21** in 84% yield. It only



21

remained to introduce the center at C_{13} to complete the construction of **3**: lithium aluminum hydride reduction of **21** ether, −78 °C) produced mostly (>20:1) one isomer.[21]

On the reasonable assumption that the process involves reduction via the cyclic chelate, the product, mp 172–173 °C, obtained after removal of the silyl protecting group (85% from

(11) Elution with 10% ether/CH_2Cl_2; R_f 0.6; $[\alpha]^{25}_D$ +18.8° (*c* 0.7, $CHCl_3$).

(12) Prepared from 2-bromopropene and 30% lithium dispersion (2% sodium) in oil.

(13) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.

(14) The pure ketone **5** (elution with CH_2Cl_2) had R_f 0.3 (CH_2Cl_2 $[\alpha]^{25}_D$ +20.6° (*c* 1.2, $CHCl_3$); NMR δ 1.38, 1.44, (s, CH_3CCH_3) 2.08 (s, $COCH_3$), 4.20 (d, $CHCOCH_3$). The less stable epimer had R_f 0.4 (CH_2Cl_2). The two methyl signals of its isopropylidene group were superposed at δ 1.36, $COCH_3$ was at δ 2.15, and $CHCOCH_3$ was in the region δ 3.3–3.8.

(15) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.

(16) Dr. David Gange has recently shown, in unpublished work from this laboratory, that the extent to which the *trans*-2,4-dimethylcyclopentanone predominates over the cis isomer depends critically on the rate of stirring during the catalytic hydrogenation. In any event, Dr. Gange has shown that the two isomers are very readily separated at the lactone stage (**11** and **16**) by crystallization from pentane, when **16** crystallizes out first. Both isomers are, of course, used in the synthesis of the final substance **3**.

(17) Lactone **16**, mp 52–55 °C, had $[\alpha]^{25}_D$ −19° (*c* 0.8, $CHCl_3$). In 12% ethyl acetate/pentane **16** and **11** had R_f 0.30 and 0.33, respectively.

(18) Collum, D. B.; McDonald, J. H.; Still, W. C. *J. Am. Chem. Soc.* **1980**, *102*, 2118.

(19) For a recent reference to diastereoselection in sulfoxide anion addition to carbonyl groups, see: Williams, D. R.; Phillips, J. G. *J. Org. Chem.* **1981**, *46*, 4101.

(20) Thick-layer chromatography (8% ether/CH_2Cl_2) gave recovered sulfoxide **6** (R_f 0.1), major adduct (R_f 0.35), minor adduct (R_f 0.65), and recovered ketone **5** (R_f 0.85). The major and minor adducts are themselves (temporarily) epimeric mixtures at C_7 and at the sulfur atom.

(21) Elution with 20% ether/CH_2Cl_2 (R_f 0.30).

21) should be correctly represented by structure 3. This has been confirmed by X-ray crystallography.[22] The structure 3 includes all the chiral centers of erythronolide A in the proper absolute configuration. The otherwise irrelevant center at C_9 must be inverted before efficient cyclization of the related hydroxy acid can be achieved (see ref 2). This is being investigated.

Registry No. 3, 79832-53-4; **5**-(β-Ac), 82281-54-7; **5**-(α-Ac), 82294-14-2; **6**, 82294-13-3; **7**, 39947-42-7; **8**, 82335-24-8; **9**, 82294-16-4; **10**, 82281-55-8; **11**, 82281-56-9; **12**-(β-OH), 82281-57-0; **12**-(α-OH), 82335-25-9; **13**-(β-isopropenyl), 82281-58-1; **13**-(α-isopropenyl), 82335-26-0; **14**, 82281-59-2; **15**, 82335-27-1; **16**, 82335-28-2; **17**-(5-α-OH), 82281-60-5; **17**-(5-β-OH), 82335-29-3; **18**-(β-isopropenyl), 82281-61-6; **18**-(α-isopropenyl), 82335-30-6; **19**-(β-isopropenyl), 82281-62-7; **19**-(α-isopropenyl), 82335-31-7; **20**, 82281-63-8; **21**, 82281-64-9; 5-methylcyclopentadiene, 96-38-8; (+)-α-pinene, 7785-70-8; 2-bromopropene, 557-93-7; 2-propenyllithium, 3052-45-7; erythronolide A, 26754-37-0.

(22) Dewan, J. C.; Lessinger, L. *Cryst. Struct. Commun.* **1981**, *10*, 1073.

(*E*)-Bicyclo[3.3.1]non-1-ene

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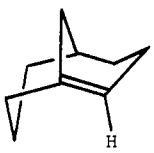
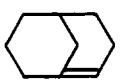
Received March 18, 1982

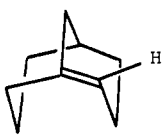
Cyclic alkenes with trans carbon–carbon double bonds have been characterized as either stable products or short-lived intermediates, depending on the ring size.[1-3] Our group and that of Marshall independently synthesized bicyclo[3.3.1]non-1-ene, **1**, a compound that is stable enough to permit isolation and



(*Z*)-1



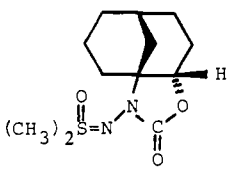
1



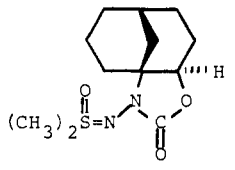
(*E*)-1

purification but much more reactive than olefins lacking strain.[4a,b] In its isolable form, **1** has the zusammen configuration, (*Z*)-**1**, as it is related in structure and stability to *trans*-cyclooctene.[4b] The geometrical isomer of **1**, the entgegen form, (*E*)-**1**, must possess appreciable strain energy because the double bond is constrained trans in the six-membered ring. Thus Kim and White failed to obtain the corresponding syn-elimination product (*E*)-**1** upon thermal decomposition of the endo-sulfoximine **2a**. However, pyrolysis of the exo-epimer **2b** gave a good yield of alkene (*Z*)-**1**.[4c]

On the basis of empirical force-field calculations, Schleyer et al. noted a relationship of alkene–parent alkane strain-energy differences (olefinic strain, OS) and the chemical stability of

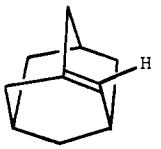


2a

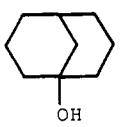


2b

several bridgehead alkenes.[5] They classified the bridgehead alkenes according to their calculated olefinic strains (kcal/mol) as isolable (OS < 17), observable (17 < OS < 21), or unstable (OS > 21). Adamantene, **3** (calculated OS = 39.5 kcal/mol),



3



4

which resembles (*E*)-**1** (calculated OS = 44.2 kcal/mol) in having an additional methylene bridge, has been detected chemically as a transient intermediate and has been observed spectrophotometrically in a cryogenic matrix.[6] The existence of *trans*-cycloalkenes with six or seven ring carbons has been demonstrated in the photochemical addition of alcohols to cyclic olefins.[7] Marshall and Kropp have attributed the stereochemical outcome of some of these reactions to an ionic addition proceeding by protonation of the highly strained photoisomer by the alcohol. Marshall and Faubl irradiated alkene **1** in water–dimethoxyethane with *p*-xylene as a triplet photosensitizer and found 30% production of the bridgehead alcohol, **4**.[4a] By analogy to earlier results, they proposed that the photohydrolysis occurred through (*E*)-**1**. In this report we present definitive evidence for the intermediacy of (*E*)-**1** in both direct and sensitized photomethanolysis of alkene (*Z*)-**1**.

Alkene (*Z*)-**1** has an ultraviolet absorption at longer wavelengths than ordinary olefins (λ_{max} (pentane) 206 nm, ϵ 7500), with a tail extending above 230 nm. This permits direct irradiation of **1** through a Vycor filter (50% transmittance at 235 nm). In a typical experiment, 192 mg of alkene (*Z*)-**1** was added to a quartz tube[8] containing 2.0 mL of dry methanol in which 3 mg of sodium had been dissolved. Making the solution basic in this manner avoided acid-catalyzed methanol addition. In a control experiment in which no radiation reached the sample, no reaction was observed. The solution was degassed by several freeze–thaw cycles and irradiated with a 450-W Hanovia lamp for 10 h at 25 °C. Gas-phase chromatography (15% OV-101) revealed 32%[9] production of 1-methoxybicyclo[3.3.1]nonane, **5**. The remainder consisted largely of unreacted olefin (65%), some dimers (*m/e* 244), and small amounts of polymer. Ether **5** was identified by comparing its 360-MHz proton NMR, IR, and mass spectra[10]

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(8) Prior to each irradiation, the quartz tube was soaked in 20% methanolic NaOH, washed with concentrated ammonia, and dried.

(9) All product yields were determined by gas chromatography relative to tetradecane as an internal standard.

(10) All NMR spectra were obtained on a Bruker WM-360 spectrometer (360 MHz). Mass spectra were run on a Finnigan 4023 GC/MS incorporating a Finnigan/INCOS 2300 data system.

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