Tetrahedron Letters,Vol.28,No.10,pp 1063-1066,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A TOTAL SYNTHESIS OF POLYETHER ANTIBIOTIC (-)-A23187 (CALCIMYCIN)+

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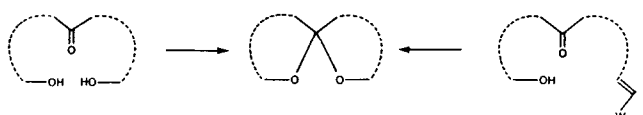
Abstraction: A total synthesis of (-)-A23187 (calcimycin) was accomplished by a convergent approach. The key step of synthesis was the stereospecific cyclization of the β-hydroxy ketone into the spiroketal under basic conditions.

For the past decade or so, polyether antibiotics have played a unique role in dramatic advances in the various areas of synthetic organic chemistry.[1,2] These include the developments of strategies and methods for the syntheses of polyfunctional acyclic systems as well as highly functionalized oxygen-containing ring systems. One of the structural characteristics found in this class of natural products is the spiroketal ring. The synthesis of this ring system is commonly achieved by ketallization of the corresponding keto diol under thermodynamically controlled conditions, i.e. A → B. This approach has proved to be very effective for the synthesis of monensin,[3] A23187,[4] narasin/salinomycin,[5] and others.[6] Nonetheless,

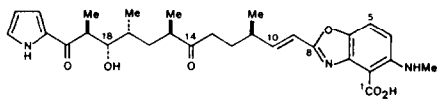


A B C

we thought it would be interesting and valuable to investigate an alternative method to control this functionality; in particular, we were intrigued by the cyclization of C → B. In this communication, we would like to report a total synthesis of A23187 (3)[7] by using such a cyclization, i.e. 1 → 3, as the key step.[8,9]

The cyclization of 1 could lead to four possible spiroketals. Of these only diastereomeric spiroketals 3 and 4 were seen as probable, given the severe destabilization of the other two isomers due to 1,3-diaxial interactions.[10] If the ring closure is allowed to reach equilibrium, the ratio of spiroketals would reflect their relative thermodynamic stability. The spiroketals 3 and 4 are structurally very similar except that 3 is stabilized by two anomeric effects[11] but has an axial methyl group at the C.11 position whereas 4 is stabilized by only one anomeric effect and has an equatorial methyl group at the C.11 position. Thus, the relative thermodynamic stability is estimated to be close but slightly favoring 4 over 3 to a small extent.[12] Under kinetic conditions, the ratio of the two possible spiroketals would reflect the ratio of the reaction rates of either 1 to form 2a or 2b, or 2a,b to form 3 or 4, depending which step is rate determining. The kinetic control of the spiro-ring formation is likely to

+Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.



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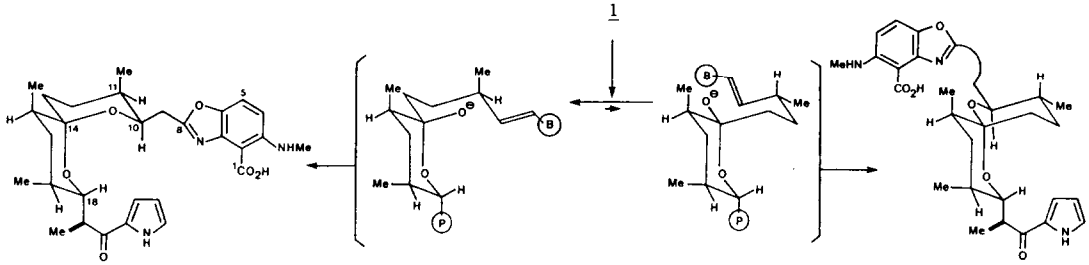
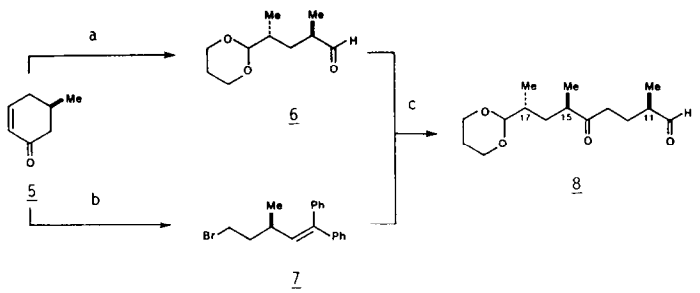


3 2a 2b 4

be a slow step[13] and the product composition depends on the relative energies of the respective transition states. It seems safe to assume that the transition state structure is closer to the hemiketal than to the spiroketal. The examples known in the literature[14] indicate that 2a should be substantially more stable than 2b. Thus, the desired product is expected to be formed preferentially.

Based on these analyses, the proposed cyclization, at least under kinetically controlled conditions, seems very promising. One additional attractive aspect of this approach is that the C.10 chiral center originates from an olefinic bond, hence the synthesis of the precursor required for this approach should be less demanding than that required for the acid-catalyzed cyclization approach, c.f. C → B versus A → B. Examination of Dreiding models suggests that the geometry of the olefinic bond would not alter the outcome of the spiroketal formation. However, because of the ease of its synthesis, we decided to test this proposed cyclization by using the trans-olefin.



Reagents, Conditions, and Yields

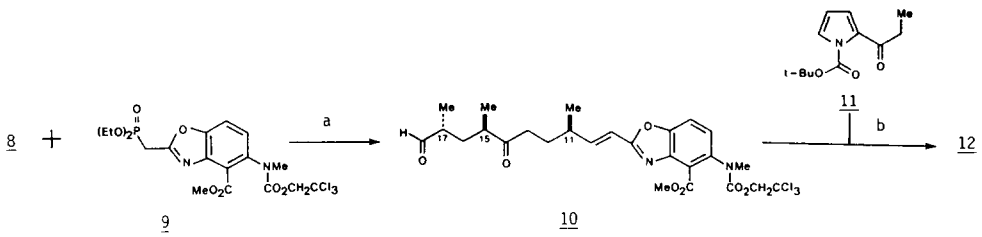
a. 1. $LiCu(Me)_2/Et_2O$/-20 °C[22] (91%) 2. MCPBA/CH_2Cl_2/0 °C (93%). 3. $PhMgBr/Et_2O$/0 °C → reflux, followed by work-up with conc. HCl/acetone/RT (93%). 4. PCC/CH_2Cl_2/RT[23] (93%) 5. $HO(CH_2)_3OH$/p-TSA/C_6H_6/reflux (97%). 6. O_3/CH_3OH-CH_2Cl_2 (2:1)/-78 °C, followed by Me_2S work-up (48%).

b. 1. i. $PhLi/Et_2O$/0 °C. ii. O_3/EtOAc/-78 °C, followed by work-up with $NaBH_4$/MeOH. iii. $NaIO_4$/THF-H_2O (85:15)/RT (56% overall yield). 2. i. $PhMgBr/Et_2O$/0 °C → RT. ii. MsCl/Et_3N/CH_2Cl_2/0 °C (overall 81% yield). 3. LiBr/DMF/100 °C (87%).

c. 1. i. 7/Mg/Et_2O/reflux. ii. RMgBr + 6/Et_2O/0 °C (overall yield 71%). 2. PCC/CH_2Cl_2/RT[23] (88% yield). 3. O_3/CH_3OH-CH_2Cl_2 (1:2)/-78 °C, followed by Me_2S work-up (58% yield).

(R)-5-Methyl-2-cyclohexen-1-one(5)[15] was converted into 6 and 7,[16] respectively, which were then coupled and transformed into the acyclic aldehyde 8. The acyclic aldehyde 8 was then reacted with the anion generated from the phosphonate 9[8] to yield a 19:1 mixture of the trans-

olefin 10 and the corresponding cis-olefin. Judging from the extensive spectroscopic studies, the C.11 methyl group retained its stereochemical purity throughout the transformation. Generation of the aldehyde at the C.18 position was accomplished in two steps, i.e. 1. $HS(CH_2)_3SH/BF_3{\cdot}Et_2O$, and 2. $CuO/CuCl_2$.[17] Under these conditions, there was no epimerization of the C.17 methyl group observed.[18] The crossed aldol reaction of the magnesium enolate, prepared from 11, with the aldehyde 10 yielded two major aldol products 12 and its stereoisomer in 61% and 16% yield, respectively. Based on the literature precedent and also on the model systems studied,[19] the desired stereochemistry was tentatively assigned to the major isomer.

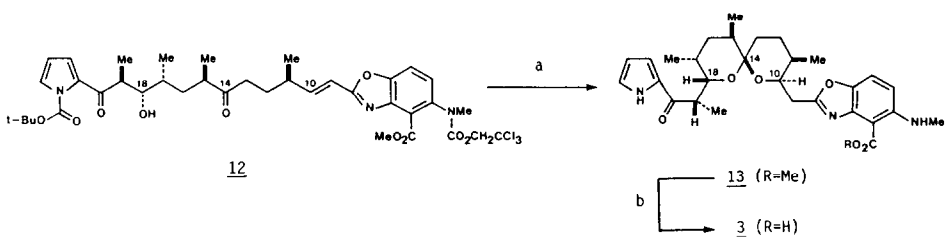


Reagents, Conditions, and Yields

a. 1. i. 9/NaH/Et_2O/0°C → 10 °C. ii. the anion + 8/Et_2O/0 °C → RT (75% of the trans olefin + 4% of the cis olefin).
2. i. $HS(CH_2)_3SH/BF_3{\cdot}Et_2O/CH_2Cl_2$/0 °C. ii. $CuO/CuCl_2/H_2O$-acetone (1:99)[17]/reflux (88% overall yield).

b. 1. 11/$(C_6H_{11})_2NMgBr$/THF/-50 °C,[19] followed by addition of 10 at 0 °C (12: 61% + stereoisomer: 16%).

The crucial cyclization was achieved by treating 12 in CH_2Cl_2/MeOH (9/1) with a catalytic amount of sodium methoxide at room temperature. By thin layer chromatographic analysis using a variety of solvent systems, only one cyclization product was observed along with some retroaldol products. The cyclization product was isolated and subjected to deprotection conditions to yield the methyl ester 13 of A23187 in 42% overall yield from the aldol product 12. The structure of 13 was unambiguously established on comparison of spectroscopic data (NMR, IR, MS, UV, α_D) with the authentic sample prepared from natural A23187.[20] The methyl ester was then hydrolyzed to A23187 (3; mp 179-182 °C, lit. 180-182 °C[7]) by using the procedure reported by Evans and coworkers.[4a] The spectroscopic data (NMR, IR, MS, UV, α_D) of the synthetic substance were superimposed on those of natural A23187.



Reagents, Conditions, and Yields

a. 1. NaOMe (cat.)/CH_2Cl_2-MeOH (9:1)/RT. 2. Zn/THF-AcOH (1:1) containing 0.25% v/v conc. HCl/RT (42% overall yield).

b. LiSPr/HMPA/RT[4a]

Regarding the stereoselectivity of the crucial cyclization, we were unable to detect any other cyclization product[21] in spite of considerable efforts to search for the minor products at the step of 12 to 13 as well as at the deprotection step of 13 to 3. Although we have not

yet established whether the cyclization was controlled by kinetic or thermodynamical sense, it is now evident that this approach is effective and efficient to construct the spiroketal ring.[24]

References and Footnotes

1) For a review on polyether antibiotics, see "Polyether Antibiotics: Naturally Occurring Acid Inophores," ed by J. W. Westley, Marcel Dekker, New York (1982), Vols. 1 and 2.
2) For reviews on synthesis of polyether antibiotics, see: a) Y. Kishi, Chap. 1 in Vol. 2 of the book quoted under reference 1. b) W. Wierenga, "The Total Synthesis of Natural Products," ed by J. ApSimon, Wiley-Interscience, New York (1981), Vol. 4, p. 263ff.
3) a) T. Fukuyama, K. Akasaka, D. S. Karanewsky, C.-L. J. Wang, G. Schmid, and Y. Kishi, J. Am. Chem. Soc., 101, 262 (1979) and preceding papers. b) D. B. Collum, J. H. McDonald, III, and W. C. Still, ibid., 102, 2120 (1980) and preceding papers. c) R. E. Ireland, D. W. Norbeck, G. S. Mandel, and N. S. Mandel, ibid., 107, 3285 (1985).
4) a) D. A. Evans, C. E. Sacks, W. A. Kleschick, and T. R. Taber, J. Am. Chem. Soc., 101, 6789 (1979). b) G. R. Martinez, P. A. Grieco, E. Williams, K. Kanai, and C. V. Srinivasan, ibid., 104, 1436 (1982) and P. A. Grieco, E. Williams, H. Tanaka, and S. Gilman, J. Org. Chem., 45, 3537 (1980). c) Y. Nakahara, A. Fujita, and T. Ogawa, J. Carbohydr. Chem., 3, 487 (1984).
5) a) Y. Kishi, S. Hatakeyama, and M. D. Lewis, "Front. Chem., Plenary Keynote Lect. IUPAC 28th Congr.," ed by K. J. Laidler, Pergamon, Oxford (1982), p. 287ff. b) Michael David Lewis, Ph. D. Dissertation, Harvard University (1983).
6) The spiroketal ring is a structural characteristic of the milbemycin-avermectin class of natural products. Extensive synthetic studies have been made on these substances. For example, see: a) S. R. Schow, J. D. Bloom, A. S. Thompson, K. N. Winzenberg, and A. B. Smith, III, J. Am. Chem. Soc., 108, 2662 (1986) and references cited therein. b) S. Hanessian, A. Ugolini, D. Dube, P. J. Hodges, and C. Andre, ibid., 108, 2776 (1986) and references cited therein.
7) M. O. Chaney, P. V. Demarco, N. D. Jones, and J. L. Occolowitz, J. Am. Chem. Soc., 96, 1932 (1974). For the absolute configuration, see reference 4a.
8) Taken from David Paul Negri, Ph. D. Dissertation, Harvard University (1980).
9) After completion of this work, Smith reported a similar approach to construct the spiroketal moiety of milbemycin β_3 [A. B. Smith, III, S. R. Schow, J. D. Bloom, A. S. Thompson, and K. N. Winzenberg, J. Am. Chem. Soc., 104, 4015 (1982)].
10) For a table listing a variety of 1,3-diaxial interaction energies, see E. J. Corey and N. F. Feiner, J. Org. Chem., 45, 765 (1980).
11) There are excellent reviews on anomeric effect. For example, see: a) P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry," Pergamon, Oxford (1983). b) A. J. Kirby, "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen," Springer-Verlag, Berlin (1983).
12) An anomeric effect in this type of ring system is estimated to be about 1.4 kcal/mol of stabilization. Applying an A-value determined on methylcyclohexane, 4 is more stable than 3 by about 0.4 kcal/mol.
13) Even if the former step is rate-determining, one will reach the same conclusion--note that 3 and 4 are formed from the same starting material.
14) For example, sorbose is known to exist as a 98:2 mixture of α-pyranose and α-furanose in deuterium oxide at 27 °C: S. J. Angyal and G. S. Bethell, Aust. J. Chem., 29, 1249 (1976). Also see, S. J. Angyal, Adv. Carbohydr. Chem., 42, 15 (1984).
15) W. Oppolzer and M. Petrzilka, Helv. Chim. Acta, 61, 2755 (1978).
16) Satisfactory spectroscopic data were obtained for all the new substances in this paper.
17) T. Mukaiyama, K. Narasaka, and M. Furusato, J. Am. Chem. Soc., 94, 8641 (1972).
18) Direct hydrolysis of the acetal even under mild acidic conditions resulted in substantial loss in the optical purity at the adjacent chiral center.
19) For crossed-aldol reactions on similar systems, see, for example, reference 5 and references cited therein. For recent reviews on aldol reactions, see: a) D. A. Evans, J. V. Nelson, and T. R. Taber, Top. Stereochem., 13, 1 (1982). b) C. H. Heathcock, "Asymmetric Synthesis," ed by J. D. Morrison, Academic Press, New York (1984), Vol. 3, p. 111ff.
20) A sample of natural A23187 was graciously provided by the Eli Lilly Company.
21) Formation of a small amount (<2% yield) of the stereoisomer could not be ruled out from this experiment.
22) H. O. House and W. F. Fischer, Jr., J. Org. Chem., 33, 949 (1968).
23) E. J. Corey and J. W. Suggs, Tetrahedron Lett., 1975, 2647.

24) Financial support from the National Institutes of Health (NS 12108) and the National Science Foundation (CHE 83-09457) is gratefully acknowledged.

(Received in USA 15 December 1986)