Synthesis of the Tricarbonyl Subunit (C_8−C_{19}) of Rapamycin via Tandem Chan Rearrangement−Oxidation

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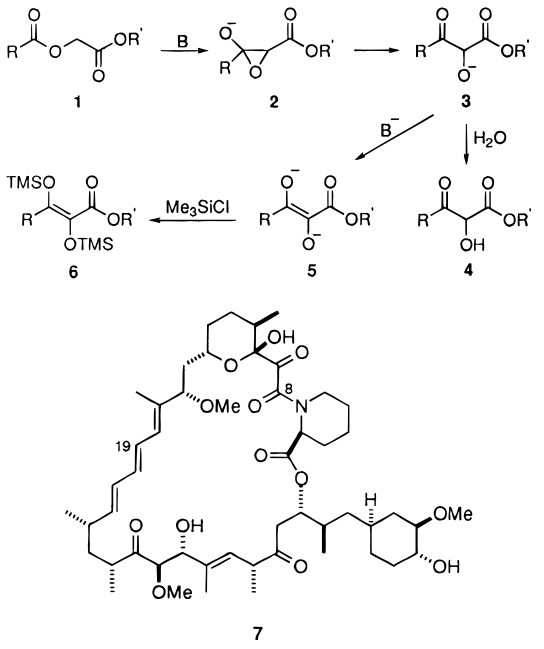
Received January 29, 1996

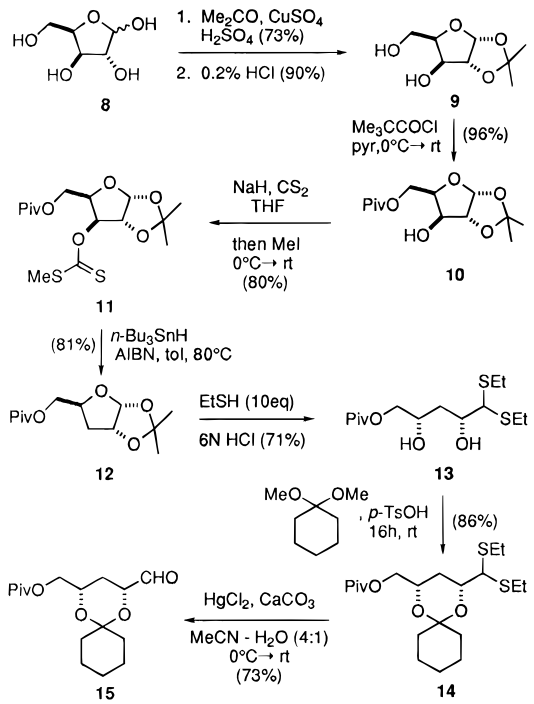
The base-induced rearrangement of α-(acyloxy)acetates **1** to α-hydroxy-β-keto esters **4** (Chan rearrangement[1]) is a convenient means for assembling an array of three contiguous oxygenated carbons. This transformation played a pivotal role in our routes to aplasmomycin[2] and boromycin,[3] but otherwise it has been rarely featured in natural product synthesis.[4] The rearrangement is believed to proceed via epoxide **2** which subsequently undergoes fragmentation to **3**. Further deprotonation of this species yields an enediolate **5** which can be trapped as the bis-silyl ether **6**. In principle, oxidation of Chan products **4** or **6** could afford a 1,2,3-tricarbonyl system, a subunit present in masked form in the important immunosuppressant rapamycin (**7**);[5] we now report an effective means for realizing this construction.[6] Specifically, we describe a synthesis of the C_8−C_{19} subunit of **7** via a tandem process involving rearrangement of an α-(acyloxy)acetate to an enediolate followed by oxidation of the derived bis-silyl ether with peracid.



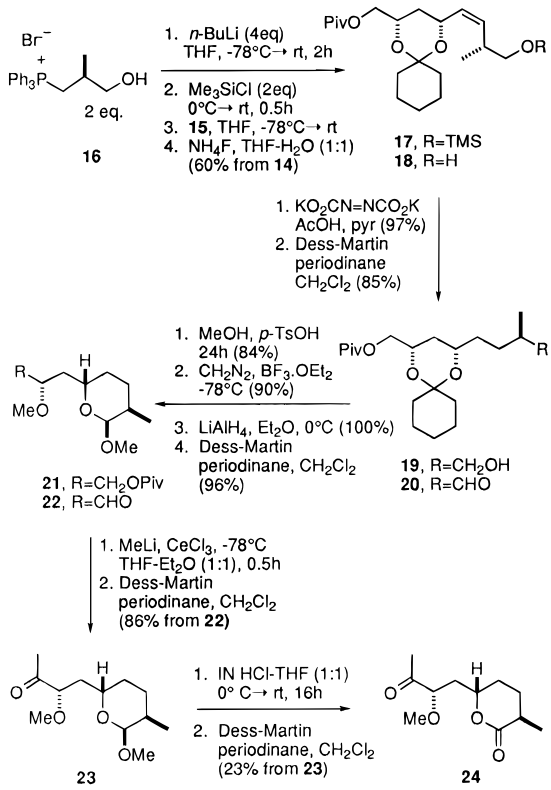
D-(+)-Xylose (**8**) was converted via its bis acetonide[7] to **9**, which was selectively protected as pivalate **10**.[8] The residual hydroxyl substituent was removed by reduction of xanthate **11** to give **12**,[9] and hydrolysis of this tetrahydrofuran derivative in the presence of excess ethanethiol yielded thioacetal **13**.[10] After protection of the diol moiety as its cyclohexylidene derivative **14**,[11] the thioacetal was hydrolyzed to afford the unstable aldehyde **15**[12] (Scheme 1).

In situ silylation of the ylide prepared from **16**,[13] followed by coupling with **15**, produced *cis*-olefin **17** which was immediately deblocked to yield **18**.[14] Reduction of this alkene with diimide[15] gave **19**, and the alcohol was oxidized with Dess−Martin periodinane[16] to **20**. Acidic

Scheme 1



Scheme 2



(1) Lee, S. D.; Chan, T. H.; Kwon, K. S. *Tetrahedron Lett.* **1984**, 3399.
(2) White, J. D., Vedananda, T. R.; Kang, M.-c.; Choudhry, S. C. *J. Am. Chem. Soc.* **1986**, *108*, 8105.
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(4) However, for a recent example, see: Holton R. A. et al. *J. Am. Chem. Soc.* **1994**, *116*, 1597.
(5) Total syntheses: (a) Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419. (b) Romo, D.; Meyer, S. D.; Johnson, D. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 7906. (c) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345. (d) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1995**, *117*, 5407.

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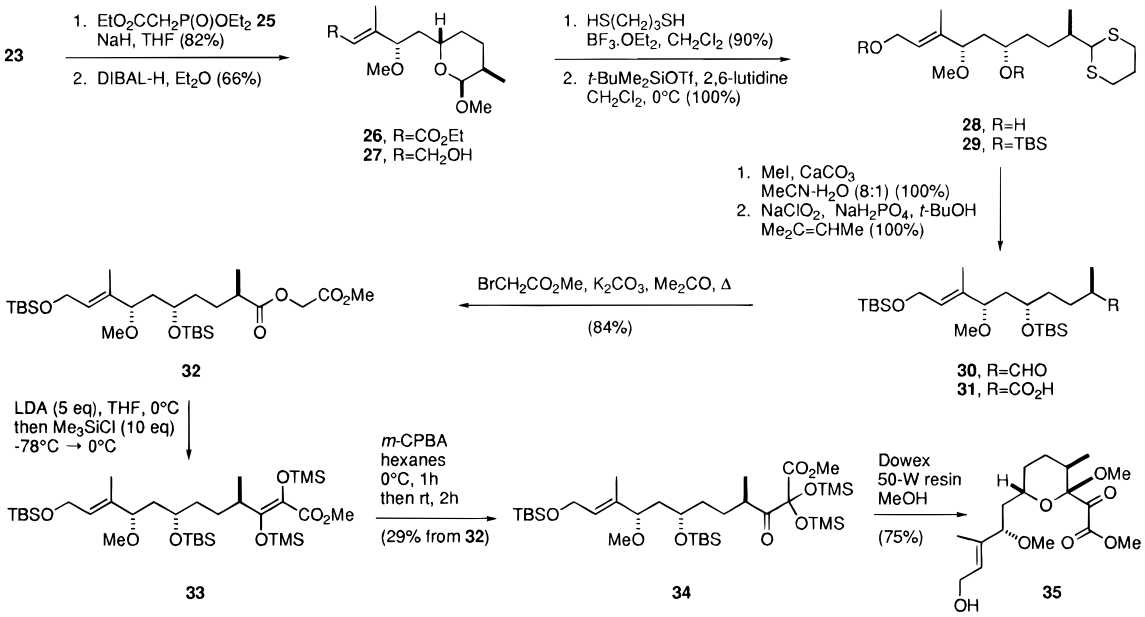
Scheme 3



methanolysis of **20** yielded a cyclic methyl acetal as a mixture of anomers (β:α = 2:1) that, after treatment with diazomethane in the presence of boron trifluoride etherate,[17] afforded methyl ether **21**. The pivalate was cleaved reductively, and the resulting alcohol was oxidized[16] to **22**. This aldehyde was transformed to ketone **23** using methyllithium−cerium trichloride[18] followed by oxidation,[16] after hydrolysis−oxidation, **23** was converted to a single δ-lactone (**24**, Scheme 2). Comparison of this substance with material obtained independently by Ley and co-workers[19] established that the two compounds were identical and thus confirmed the configurational assignments made to **24**.

Condensation of **23** with the anion of phosphonate **25**[20] gave a 14:1 mixture of (*E*)-α,β-unsaturated ester **26** and its (*Z*) isomer. The mixture was reduced,[21] and (*E*)-alcohol **27** was obtained pure after chromatography. Exposure of **27** to 1,3-propanedithiol in the presence of a Lewis acid[22] yielded dithiane **28** which was then protected as its bis silyl ether **29**.[23] Removal of the dithiane[24] furnished aldehyde **30**, and this was oxidized[25] to carboxylic acid **31**. Coupling of the potassium salt of **31** with methyl bromoacetate gave **32** which underwent Chan rearrangement with excess LDA followed by silylation of the intermediate enediolate to afford **33** as a single isomer that was unstable to chromatography on silica. Oxidation of this substance with *m*-chloroperbenzoic acid in hexanes led directly to **34**, presumably via rearrangement of an intermediate epoxide,[26] in 29% isolated yield from **32**. Final removal of the four silyl ethers in methanol over an acidic resin produced cyclic ketal **35**[27] as a single anomer (Scheme 3).

In summary, the chemistry outlined in Schemes 1−3 defines a new route to a key segment of rapamycin. Improvement of the Chan rearrangement−oxidation[28] of **32** and incorporation of this sequence into a total synthesis of **7** will be the subject of further studies.

Acknowledgment. We are indebted to Professor Steven Ley and Michael Willis, Cambridge University, for ^1H and ^{13}C NMR spectra of **24**. This research was assisted financially by the National Institutes of Health through Grant No. GM50574.

Supporting Information Available: Preparative procedures and characterization data for all new compounds (21 pages).

JO960176C

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(28) Chan rearrangement of **32** to **33** is accompanied by the formation of carboxylic acid **31**, particularly when bases other than LDA are employed. Although the epoxidation of **33** takes place in high yield, major losses are incurred in the purification of **34** by chromatography on silica.