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AN APPLICATION OF THE EVANS-PRASAD 1,3-SYN DIOL SYNTHESIS TO A STEREOSPECIFIC SYNTHESIS OF THE C_{10}-C_{27} SEGMENT OF RAPAMYCIN

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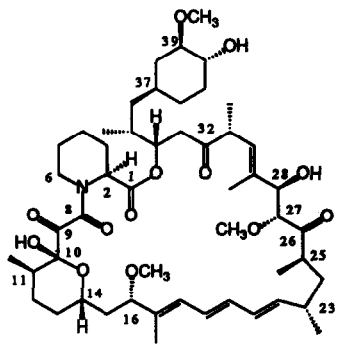
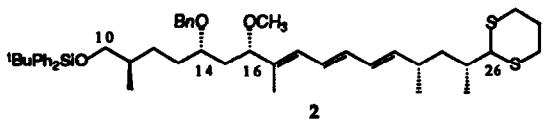
Abstract: An efficient regioselective and stereoselective approach to the C_{10}-C_{27} fragment of rapamycin is described.

Recently we have described our approach to the total synthesis of rapamycin (**1**), an immunosuppressant of high potency and novel mechanism of action.[1-4] One of the fragments synthesized in that exploratory study was the triene dithiane **2**.[2] While the methodology employed in that effort was useful in providing material for early chemical evaluation, there was, as reported, a serious weakness in the constuction of **2** in that no control was excercised over the stereochemistry at C_{16}. A key reaction in the gross construction of **2** was the Nozaki-Kishi coupling of **3** + **4** (Scheme I).[5,6] Unfortunately, this reaction produced a stereorandom mixture of C_{16} epimers **5**. Moreover, and not surprisingly, a variety of attempted reductions of derived ketone **6** bearing the β-benzyloxy group also provided virtually 1:1 mixtures of epimers **5**.

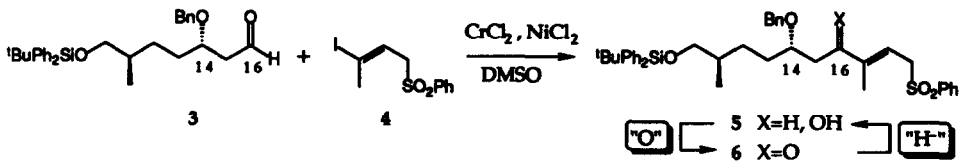


1 rapamycin



2

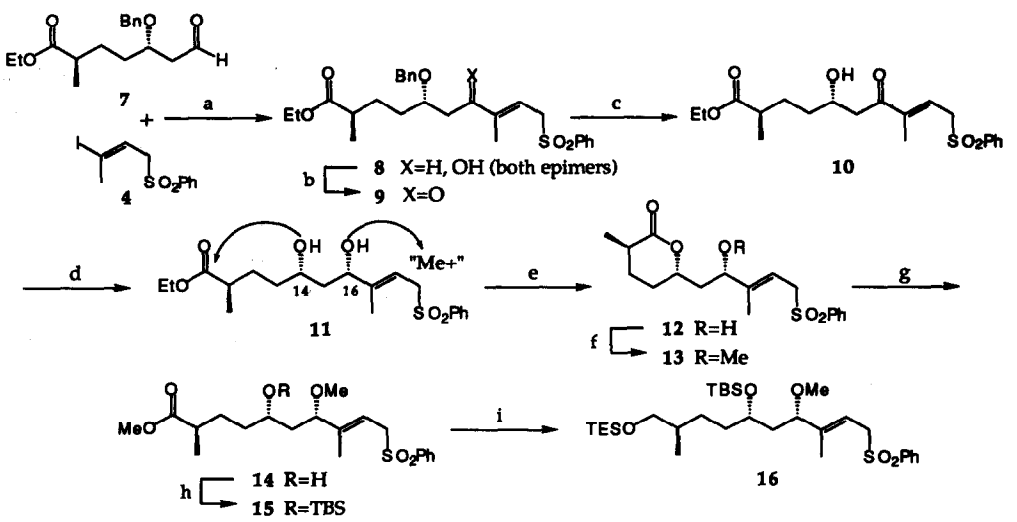
SCHEME I



3 **4**

A solution to the stereochemical problem at C_{16} was in principle inherent from the Evans[7]-Prasad[8] route to 1,3-"syn"diols (via the reduction of β-hydroxyketones with sodium borohydride-methoxydiethylborane). Two potentially serious problems presented themselves in applying this technology to our needs. The first was that of finding an opportunity where the functionality in the molecule would be compatible with the unveiling of a free C_{14} hydroxyl group needed to provide the stereochemical guidance in the reduction of the C_{16} ketone. The logic of our synthesis virtually demanded that, prior to its exposure, the C_{14} hydroxyl had been durably protected (such as via a benzyl ether). Another problem was that of preserving regiochemical control in distinguishing the C_{14} directing hydroxyl group from the hydroxyl function which would be developed at C_{16} from ketone reduction. This differentiation was necessary for accomplishing specific methyl ether formation at carbon 16. Related and gratifyingly straightforward solutions to both problems are reported in this *Letter*. These findings are provided in the context of the synthesis of the highly advanced intermediate **21** which encompasses carbons 10-27 of rapamycin in functionally differentiated form.

SCHEME II



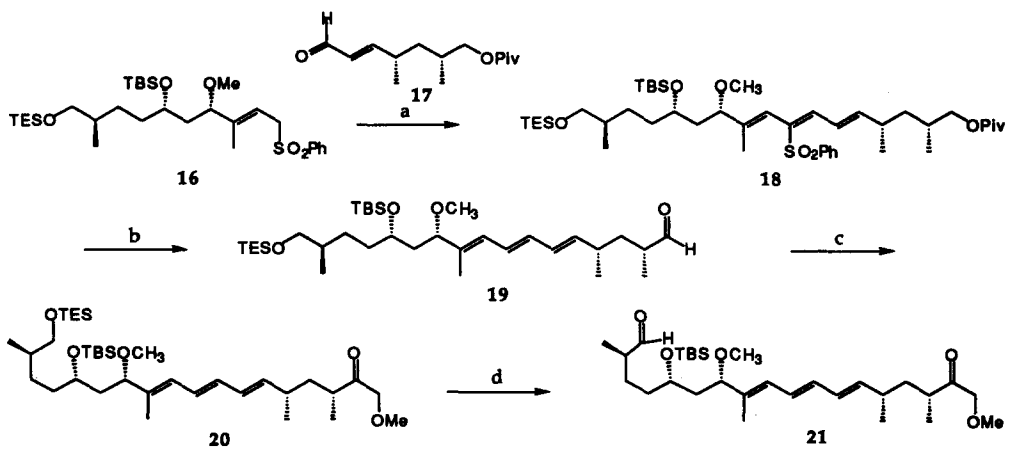
(a) $NiCl_2$, $CrCl_2$, **4**, DMSO, 25°C. (b) Dess-Martin periodinane, CH_2Cl_2, 25°C. (c) BCl_3, CH_2Cl_2, -78°C, 75% from **7**. (d) Et_2BOMe, $NaBH_4$, $PhCH_3$, -78°C. (e) i) LiOH, THF/MeOH/H_2O, 0°C; ii) EDCI, CH_2Cl_2, 25°C, 71% from **10**. (f) Ag_2O, MeI, 25°C. (g) K_2CO_3, MeOH, 25°C. (h) TBSOTf, 2,6-lutidine, 0°C, 86% from **12**. (i) i) DIBAL-H, THF, 0°C; ii) TESCl, Et_3N, CH_2Cl_2, 86%.

Ester aldehyde **7**, obtained by deprotection of its previously described dithiane derivative, was coupled with **4** to give the now expected 1:1 mixture of epimers which, on oxidation, converge to afford enone **9** (Scheme II). Amazingly, the free alcohol **10**, a β-aldol, could be obtained in 89% yield by treatment of **9** with BCl_3. The Evans-Prasad reduction of **10** afforded a 94% yield of **11**. The advantage of starting with a ester function at the terminus was now exploited. Lactonization of the derived hydroxyacid (obtained by the action of OH^- on **11**) served to distinguish the C_{14} and C_{16} oxygens (see compound **12**) . Methylation of the free hydroxyl group of **12** was accomplished (without opening of the lactone)[9] to afford **13**. The latter, upon methanolysis, provided **14** and **16**.

Julia coupling of **16** with **17**[10] followed by (i) acetylation, (ii) β-elimination, (iii) reduction of the pivalate, (iv) reductive elimination of the acetoxysulfone and (v) oxidation of the primary alcohol afforded **19**, which was converted in straightforward steps to **21** (Scheme III).

It will be recalled that a degradative scheme starting with rapamycin had also produced this compound (**21**)[11]. Indeed, the identity of the infrared, ^1H NMR and ^{13}C NMR spectra of the totally synthetic and degradation derived materials served to validate the assignment of both the degradation and synthetic routes fully.

SCHEME III



(a) i) LDA, **17**, THF, -78°C; ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 25°C; iii) DBU, THF, 25°C, 89%. (b) i) DIBAL-H, $PhCH_3$, 0°C; ii) Na(Hg), KH_2PO_4, THF/MeOH, -20°C; iii) Dess-Martin periodinane, pyridine, 25°C, 67%. (c) i) $LiCH_2OCH_3$, Et_2O, -78°C; ii) Dess-Martin periodinane, pyridine, CH_2Cl_2, 25°C, 77%. (d) i) AcOH/THF/H_2O, 25°C; ii) Dess-Martin periodinane, pyridine, CH_2Cl_2, 86%.

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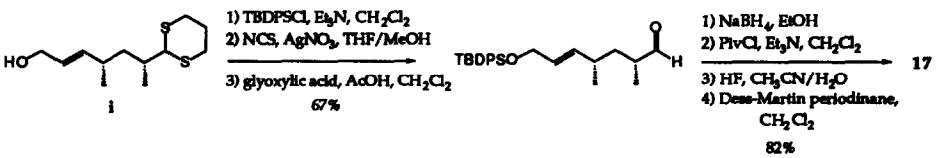
References.

† Formerly published as Cheryl D. Myers.

1. Fisher, M. J.; Myers, C. D.; Joglar, J. ; Chen, S.-H.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5826.
2. Chen, S.-H.; Horvath, R. F. ; Joglar, J.; Fisher, M. J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5834.
3. For other synthetic efforts on rapamycin, see: Hale, M. R.; Hoveyda, A. H. *J. Org. Chem.* **1992**, *57*, 1643. Meyer, S. D.; Miwa, T.; Nakatsuka, M.; Schrieber, S. L. *J. Org. Chem.* **1992**, *57*, 5058. Romo, D.; Johnson, D. D.; Plamondon, L.; Miwa, T.; Schrieber, S. L. *J. Org. Chem.* **1992**, *57*, 5060. Sin, N.; Kallmerten, J. *Tetrahedron Lett.* **1993**, *34*, 753.
4. For a total synthesis of rapamycin, see: Piscopio, A. D.; Minowa, N.;Chakraborty, T. K.; Koide, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1993**, 617. Nicolaou, K. C.; Bertinato, P.; Piscopio, A. D.; Chakraborty, T. K.; Minowa, N. *J. Chem. Soc. Chem. Commun.* **1993**, 619. Nicolaou, K.C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.*, in press.
5. Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.
6. Takai, K.; Kimera, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.
7. Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866.
8. Chen, K.-M.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, H. J. *Tetrahedron Lett.* **1987**, *28*, 155.
9. Attempted methylation of **12** with methyl triflate resulted in a mixture of products derived from methylation of the lactonic oxygen.
10. Aldehyde **17** was prepared from **i**[2] by the following method:



11. Yohannes, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1992**, *33*, 7469.

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