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Studies directed towards the synthesis of antascomicin A: stereoselective synthesis of the C1–C21 fragment of the molecule☆

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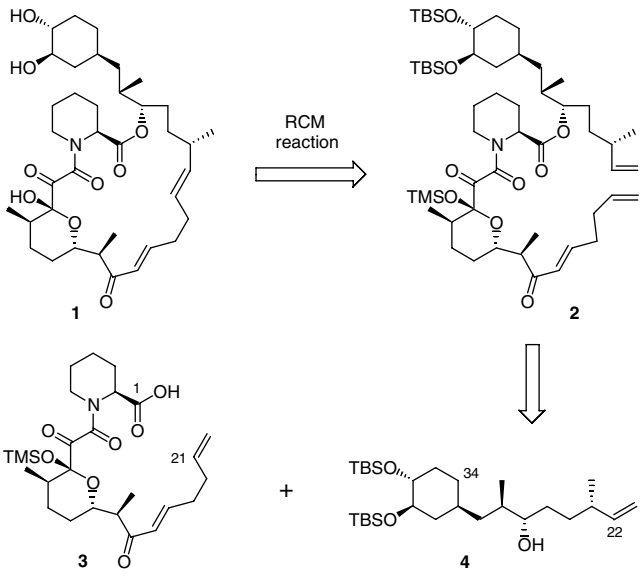
Abstract—A stereoselective synthesis of the C1–C21 fragment of the non-immunosuppressive immunophilin-binding natural product, antascomicin A was achieved using, as key steps, highly stereoselective Aldol reactions to build the C1–C17 fragment and a Nozaki–Hiyama–Kishi reaction to couple it with the remaining C18–C21 moiety.

Antascomicins are produced by fermenting a strain of the genus *Micromonospora* isolated from a soil sample collected in China.[1] The binding affinity of antascomicins to FKBP12 ($IC_{50} = 2$ nm, for antascomicin A, **1**) is very similar to that of FK506 or rapamycin (1.1 and 0.6 nm, respectively) in the same binding assay, but antascomicins do not show any immunosuppressive activity. Non-immunosuppressive immunophilin binding ligands such as antascomicins hold a lot of promise for the treatment of various neuro-degenerative disorders like Alzheimer's and Parkinson's diseases.[2] We envisaged that the total synthesis of these molecules would not only provide an access to larger quantities necessary for further biological studies, but also help to design and build more potent synthetic analogues. The total syntheses of antascomicin B[3] and the C18–C34 fragment of antascomicin A[4] have been reported. As part of our ongoing studies directed towards the synthesis of various immunosuppressants, we investigated the total synthesis of antascomicin A.

An RCM[5] approach was contemplated to construct the macrocyclic ring of antascomicin A. Retrosynthetic analysis (Scheme 1) reveals that an acyclic precursor such as **2** was ideally suited to carry out the planned RCM reaction. Triene **2** could be easily assembled by coupling the C1–C21 unit **3** with the C22–C34 fragment **4**.

In this letter, we describe the stereoselective synthesis of the C1–C21 fragment of antascomicin A.[6] Schemes 2–4 outline the details of the synthesis of this desired fragment. Asymmetric Aldol addition of the titanium enolate derived from *N*-propanoyl oxazolidinethione **5**[7] (Scheme 1) to aldehyde **6**, prepared by oxidation of mono benzyl-protected pentane-1,5-diol, gave the 'non-Evans' *syn* Aldol product **7** as the only isolable diastereomer in 78% yield. The relative and absolute stereochemistry of the product was assigned on the basis of an



Scheme 1. Retrosynthetic analysis of antascomicin A (**1**).

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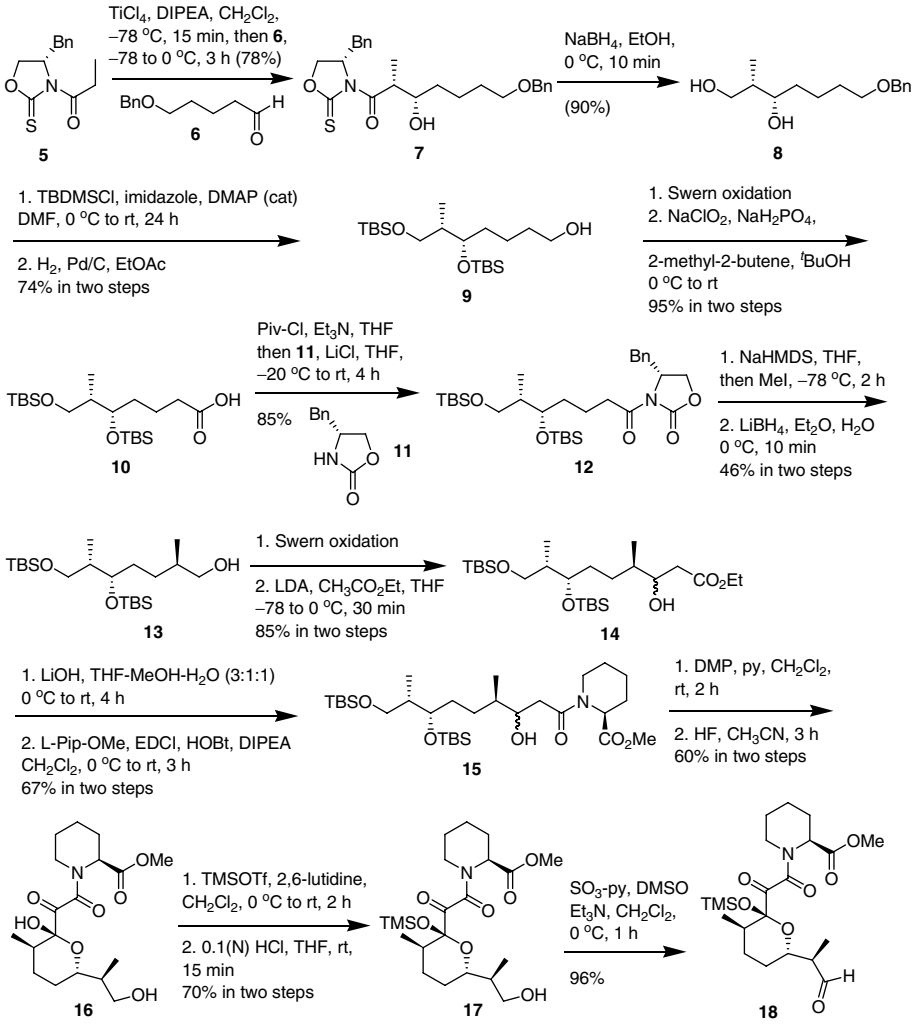
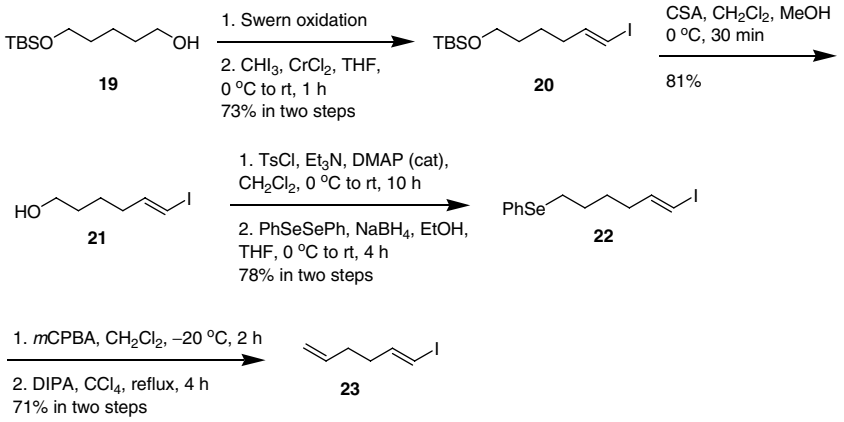


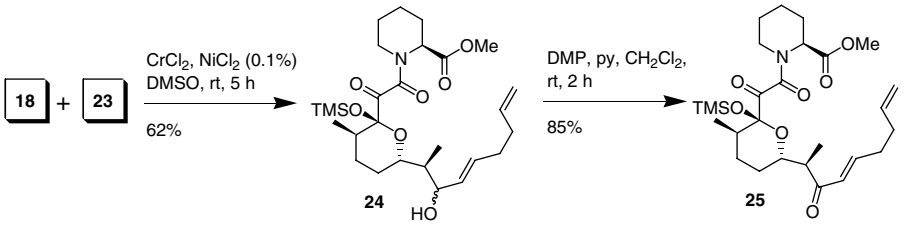
Scheme 2. Stereoselective synthesis of the C1–C16 fragment **18**.



Scheme 3. Synthesis of the C17–C21 fragment **23**.

earlier reported work.[8] The *syn*-relationship between the newly generated chiral centres was supported by the relatively small value of the corresponding vicinal coupling constant of 2.97 Hz.

Reductive removal of the chiral auxiliary using $NaBH_4$ gave an intermediate diol **8** that was subjected to disilylation to furnish the di-TBS ether and finally debenzylation by hydrogenation gave **9** in 68% yield from **8**. A two-step oxidation protocol was followed to oxidize the alcohol **9** to acid **10** in 95% overall yield. Compound **10** was used to carry out N-acylation of the chiral oxazolidinone **11**, derived from D-Phe, under the mixed anhydride method[9] to furnish **12** in 85% yield. Diastereoselective



Scheme 4. Coupling of the C1–C16 (**18**) and C17–C21 (**23**) fragments.

alkylation of the Na-enolate of **12** with MeI was followed by reductive removal of the chiral auxiliary to give alcohol **13** as the only isomer in 46% overall yield. Swern oxidation[10] of **13** gave an intermediate aldehyde, which was reacted with the Li-enolate of ethyl acetate to give the β-hydroxy ester **14** as a mixture of diastereoisomers in 85% yield. Saponification of **14** and subsequent coupling with L-pipecolic acid methyl ester furnished the amide **15** in 67% overall yield.

Oxidation of the β-hydroxy amide **15** with Dess–Martin periodinane (DMP)[11] gave a '1,2,3-triketo' intermediate,[12] which was subjected to desilylation resulting in the spontaneous formation of the hemiketal **16** in 60% yield. Disilylation of **16** gave a di-TMS–ether intermediate. Brief exposure of this intermediate di-TMS–ether to mild acid selectively deprotected the primary hydroxyl group to furnish the TMS–ether of the hemiketal **17** in 70% yield. Finally oxidation of **17** gave the aldehyde **18** in 96% yield.

Synthesis of the C19–C21 fragment started with the mono-TBS ether of pentane-1,5-diol **19** (Scheme 3). Swern oxidation of **19** followed by a Takai reaction[13] furnished the vinyl iodide **20** in 73% yield. Acid-catalyzed desilylation of **20** gave **21** in 81% yield. Tosylation of **21** was followed by nucleophilic substitution of the tosylate group by $PhSe^-$, generated in situ by sodium borohydride reduction of diphenyl diselenide,[14] giving the phenylselenide **22**, in 78% overall yield, which was then subjected to an oxidation–elimination process. Oxidation of selenide **22** using *m*CPBA and subsequent β-elimination of the resulting selenoxide furnished the diene **23** in 71% yield.

Coupling of the C1–C16 (**18**) and C17–C21 (**23**) fragments to build the target C1–C21 moiety is shown in Scheme 4. A Nozaki–Hiyama–Kishi coupling[15] was employed to carry out the coupling, giving the coupled product **24** in 62% yield as a mixture of isomers. Finally, Dess–Martin oxidation[11] of **24** furnished dienone **25**,[16] the target C1–C21 fragment of antascomicin A, in 85% yield.

Further work is now in progress to complete the total synthesis of antascomicin A (**1**).

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References and notes

1. Fehr, T.; Sanglier, J.-J.; Schuler, W.; Gschwind, L.; Ponelle, M.; Schilling, W.; Wioland, C. *J. Antibiot.* **1996**, *49*, 230–234.
2. (a) Snyder, S. H.; Sabatini, D. M.; Lai, M. M.; Steiner, J. P.; Hamilton, G. S.; Suzdak, P. D. *Trends Pharmacol. Sci.* **1998**, *19*, 21–26; (b) Steiner, J. P.; Connolly, M. A.; Valentine, H. I.; Hamilton, G. S.; Dawson, T. M.; Hester, L.; Snyder, S. H. *Nat. Med.* **1997**, *3*, 421–428; (c) Hamilton, G. S.; Huang, W.; Connolly, M. A.; Ross, D. T.; Guo, H.; Valentine, H. L.; Suzdak, P. D.; Steiner, J. P. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1785–1790.
3. Brittain, D. E. A.; Griffiths-Jones, C. M.; Linder, M. R.; Smith, M. D.; McCusker, C.; Barlow, J. S.; Akiyama, R.; Yasuda, K.; Ley, S. V. *Angew. Chem., Int. Ed.* **2005**, *44*, 2732–2737.
4. Fuwa, H.; Okamura, Y.; Natsugari, H. *Tetrahedron* **2004**, *60*, 5341–5352.
5. (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450; (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013–3043; (c) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29; (d) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527.
6. For our synthesis of the C22–C34 fragment of antascomicin A see the following paper.
7. (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883–7884; For some earlier leading references of the oxazolidinethione based Aldol reactions giving 'non-Evans' *syn* products see: (b) Fujita, E.; Nagao, Y. *Adv. Heterocycl. Chem.* **1989**, *45*, 1–36; (c) Mukaiyama, T.; Kobayashi, S. *Org. React.* **1994**, *46*, 1–103.
8. (a) Chakraborty, T. K.; Jayaprakash, S.; Laxman, P. *Tetrahedron* **2001**, *57*, 9461–9467; (b) Delaunay, D.; Toupet, L.; Le Corre, M. *J. Org. Chem.* **1995**, *60*, 6604–6607.
9. Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775–7778.
10. Mancuso, A. J.; Swern, D. *Tetrahedron Lett.* **1981**, *35*, 2473–2476.
11. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.
12. Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R. *Tetrahedron Lett.* **1993**, *34*, 167–170.
13. Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408–7410.
14. (a) Reich, H. J.; Wollowitz, S.; Trend, J. E.; Chow, F.; Wendelborn, D. F. *J. Org. Chem.* **1978**, *43*, 1697–1705; (b) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 1396–1403.
15. (a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284; (b) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644–5646; For reviews, see: (c) Cintas, P. *Synthesis* **1992**, 248–257; (d) Hashmi, A. S. K. *J. Prakt. Chem.* **1996**, *338*, 491–495; (e) Wessjohann, L. A.; Scheid, G. *Synthesis* **1999**, 1–36; (f) Fürstner, A. *Chem. Rev.* **1999**,

99, 991–1045; (g) Fürstner, A. *Chem. Eur. J.* **1998**, *4*, 567–570.

16. Data of **25** $R_f = 0.55$ (SiO_2, 20% EtOAc in petroleum ether); $[\alpha]_D^{27} - 4.0$ (*c* 0.058, $CHCl_3$); IR (KBr): ν_{max} 2930, 1741, 1646, 1448, 1249, 1039, 845 and 758 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 6.89 (m, 1H, C18–*H*), 6.19 (d, $J = 15.7$, 1H, C17–*H*), 5.80 (m, 1H, C23–*H*), 5.27 (d, $J = 5.4$ Hz, 1H, C2–*H*), 5.05 (dd, $J = 15.6$, 1.7 Hz, 1H, C24–H_a), 5.01 (dd, $J = 10.2$, 1.5 Hz, 1H, C24–H_b), 4.04 (m, 1H, C14–*H*), 3.78 (s, 3H, $-CO_2CH_3$), 3.44 (ddd, $J = 14.4$, 2.9, 1.2 Hz, 1H, C6–H_a), 3.28 (ddd, $J = 14.4$, 11.5, 2.9, 1H, C6–H_b), 2.88 (m, 1H, C15–*H*), 2.36–2.25 (m, 4H, C19–H_2, C20–H_2), 2.25–2.20 (m, 2H, C5–H_2), 1.85–1.40 (m, 9H, C3–H_2, C4–H_2, C11–*H*, C12–H_2, C13–H_2), 1.16 (d, $J = 6.9$ Hz, 3H, C15–CH_3), 0.77 (d, $J = 6.5$ Hz, 3H, C11–CH_3), 0.17 (s, 9H, $Si(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.16, 197.18, 170.55, 166.74, 146.67, 136.86, 129.66, 115.50, 102.23, 76.57, 71.66, 56.00, 52.07, 51.60, 48.64, 44.34, 36.03, 32.00, 29.36, 26.57, 24.70, 21.15, 15.43, 12.39, 1.66; Mass (ESIMS): *m*/*z* 544 $[M+Na]^+$; HRMS (ESIMS): calcd for $C_{27}H_{43}NO_7SiNa$ $[M+Na]^+$: 544.2706, found: 544.2718.