

Studies of fragment assembly aldol reactions of chiral aldehydes and chiral methyl ketones: stereoselective synthesis of the C(13)–C(25) segment of scytophycin C

William R. Roush* and Garrett J. Dilley

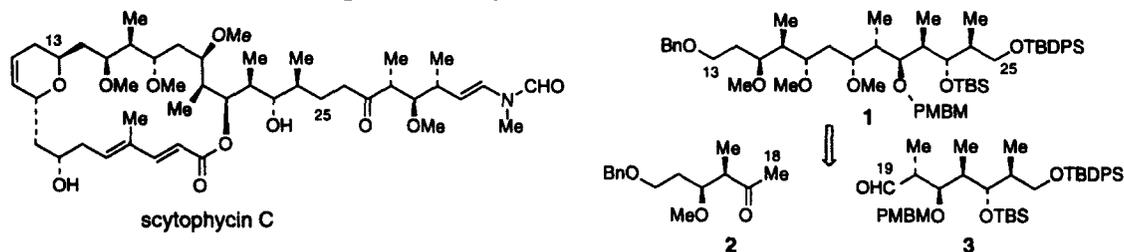
Department of Chemistry, University of Michigan, Ann Arbor, MI 48109, USA

Received 5 April 1999; revised 26 April 1999; accepted 27 April 1999

Abstract

A highly stereoselective synthesis of the C(13)–C(25) fragment of scytophycin C is described, along with stereochemical studies of the key fragment assembly methyl ketone aldol reaction. © 1999 Elsevier Science Ltd. All rights reserved.

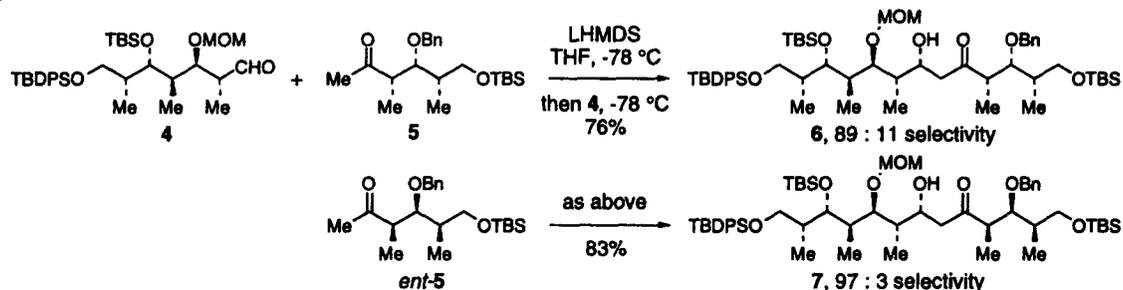
Scytophycin C is an important member of a family of biologically active macrolides isolated from the terrestrial blue-green alga *Scytonema pseudohofmanni*.^{1,2} In addition to its broad spectrum antifungal activity, scytophycin C has demonstrated significant activity against solid tumors in vitro.³ The potent biological properties of scytophycin C, its scarce abundance from natural sources, and its close structural resemblance⁴ to the marine natural product swinholide A^{5,6} has stimulated considerable interest in its synthesis.^{7–11} An elegant total synthesis of scytophycin C has been recorded by Paterson,^{7–9} and both Paterson and Nicolaou have completed total syntheses of swinholide A.^{12–14}



We were attracted to the possibility that the C(13)–C(25) segment, 1, of scytophycin C could be assembled by the aldol reaction of the chiral methyl ketone 2 and the chiral aldehyde 3. In previous studies of methyl ketone fragment assembly aldol reactions we demonstrated that the stereoselectivity is dependent on the nature of the metal enolate as well as the 2,3-stereochemistry of the aldehyde and

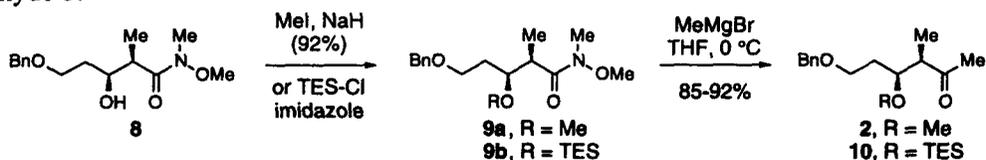
* Corresponding author.

the aldehyde β -alkoxy protecting group.¹⁵ As a general rule, we have found that the best selectivity for the *syn*-(Felkin)aldol diastereomer is obtained with 2,3-*anti*-aldehydes when lithium enolates are used, and that silyl ether protecting groups for the aldehyde β -hydroxyl unit leads to diminished selectivity.¹⁵ Moreover, although the diastereoselectivity of fragment assembly aldol reactions is expected to be dependent on the intrinsic diastereofacial selectivity preferences of both components,¹⁶ we have observed that the methyl ketone enolate exerts only a modest diastereofacial bias and therefore that the aldehyde fragment dominates the stereochemical outcome of the reaction.

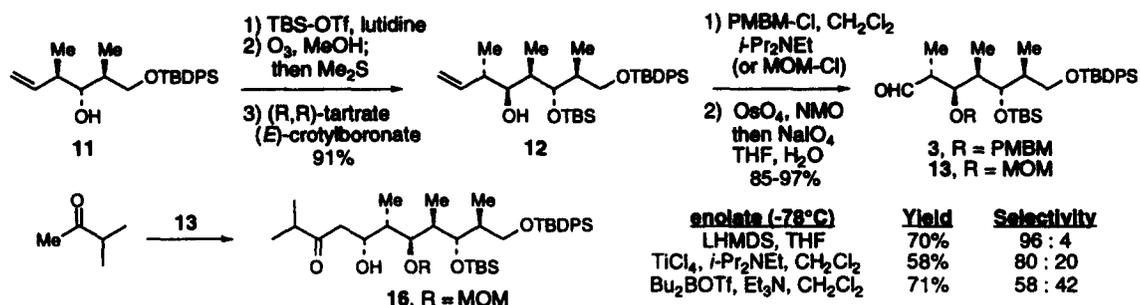


For example, in the (mismatched) aldol coupling of **4** and **5**, diastereomer **6** predominates with 89:11 selectivity.¹⁵ On the other hand, when the lithium enolate of the enantiomeric methyl ketone, *ent*-**5**, is used, aldol **7** is the near exclusive product (97:3 ds).¹⁷ Accordingly, we anticipated that the aldol reaction of **2** and **3** would occur with excellent selectivity, since this combination is homochirally paired with the *4/ent*-**5** combination.

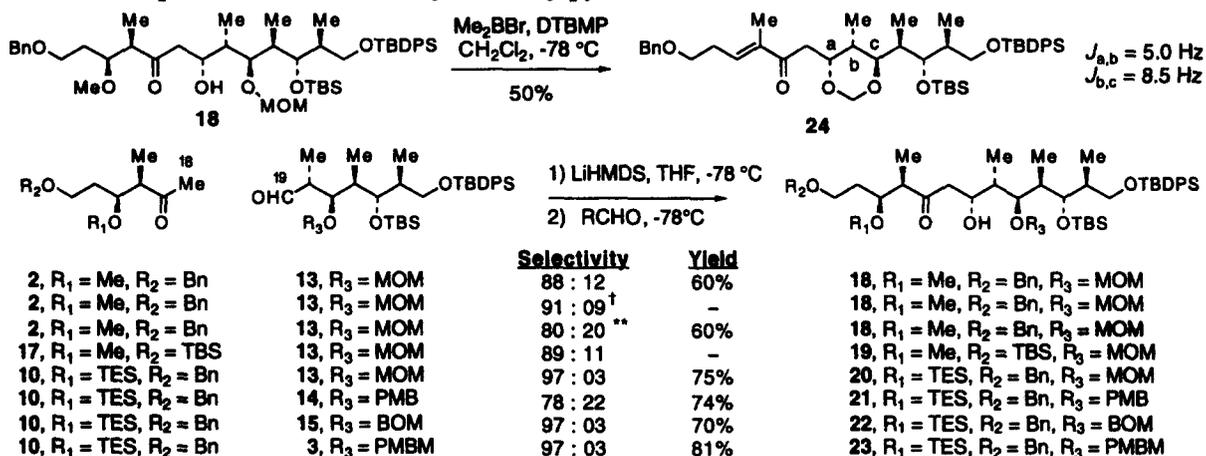
Methyl ketone **2** was synthesized in a straightforward manner starting from the known Weinreb amide **8**.¹⁸ Thus, methylation of the hydroxyl group of **8** followed by treatment of the resulting ether **9a** with MeMgBr in THF provided **2** in excellent yield.¹⁹ The corresponding TES ether, **10**, was also synthesized from the known TES ether **9b**.¹⁸ Aldol reactions of **2** with isobutyraldehyde indicated that these ketones would exert, at best, a very modest influence on the diastereoselectivity of subsequent aldol reactions with aldehyde **3**.²⁰



Aldehyde **3** was synthesized from the known homoallylic alcohol **11**.²¹ Protection of the secondary hydroxyl group as a TBS ether followed by ozonolysis of the vinyl group gave an aldehyde that was subjected to standard diastereoselective crotylboration conditions,²¹ thereby providing **12** in excellent yield. The hydroxyl group of this intermediate was then protected as a (*p*-methoxybenzyloxy)methyl (PMBM) ether.²² Oxidative cleavage of the double bond then provided the targeted aldehyde **3**. Several other aldehyde substrates containing C(21)-MOM (**13**), PMB (**14**), and BOM ethers (**15**) were synthesized analogously.

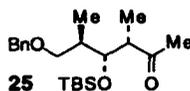


Results of aldol reactions of 13 with isopropyl methyl ketone confirmed our expectation that the Felkin diastereofacial selectivity would be best in experiments using lithium enolates. Consequently, we concentrated almost exclusively on use of lithium enolates in our studies of the fragment assembly aldol reaction of the two chiral fragments. Surprisingly, in spite of the fact that aldehyde 13 displays a 96:4 diastereofacial preference in its reaction with the lithium enolate of isopropyl methyl ketone, and the fact that 2 and 13 are in the same stereochemical series as *ent*-5 and 4, respectively, the reaction of 13 and the lithium enolate of 2 provided aldol 18 with a disappointing selectivity of 88:12. The stereochemistry of 18 was verified by conversion to the methylene acetal 24 upon treatment with Me₂BBr in CH₂Cl₂ at -78°C in the presence of 2,6-di-*t*-butyl-4-methylpyridine (DTBMP).^{23,24}



[†]Reaction performed in presence of HMPA. ^{**}Reaction performed with the sodium enolate (NaHMDS, THF, -78 °C)

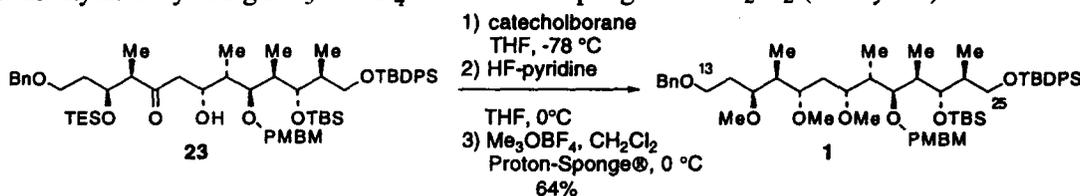
Because we had previously presented evidence that chelation of the δ -benzyl ether protecting group of 25 to the lithium ion reaction center plays a role in the aldol diastereoselectivity of this methyl ketone,^{25,26} aldol reactions of 13 and the lithium enolate of 2 were performed in the presence of HMPA and also with the sodium enolate of 2 (entries 2 and 3).



The reaction diastereoselectivity increased slightly to 91:9 when the reaction was performed in the presence of HMPA, and decreased to 80:20 in the sodium enolate experiment. Moreover, when the C(13) benzyl ether unit of 2 was replaced by the TBS ether in methyl ketone 17, the lithium enolate aldol stereoselectivity was essentially unchanged relative to the original case (compare entries 1 and 4). While these data tended to rule out involvement of the δ -benzyl ether as a chelating group in the case of 2, it was conceivable that C(15)-methyl ether might play such a role. Therefore, aldol reactions of methyl

ketone **10** containing a C(15)-OTES ether were performed. To our considerable delight, the aldol reaction of **13** and the lithium enolate of **10** proceeded with excellent selectivity (97:3) and provided aldol **20** in 75% isolated yield. In anticipation that removal of the C(21)-MOM ether in **20** could prove problematic later in the synthesis, our attention turned to the identification of a more appropriate protecting group for the C(21) hydroxyl group. A *p*-methoxybenzyl ether (PMB) seemed ideal, since it is readily removed by oxidation with DDQ under relatively mild conditions.²⁷ Surprisingly, however, the aldol reaction of **10** and aldehyde **14** exhibited significantly diminished selectivity (78:22). We currently do not have an acceptable explanation for this turn of events. However, excellent stereoselectivity (97:3) returned when aldehydes **15** (with a C(21)-BOM ether) and **3** (with a C(21)-PMBM ether) were used as substrates for the key aldol reaction.²⁸

Completion of the synthesis of the scytophycin C(13)–C(25) fragment, **1**, involved reduction of **23** with catecholborane in THF at -78°C affording the *syn*-1,3-diol with excellent diastereoselectivity.²⁹ Selective deprotection of the C(15)-TES ether provided the corresponding triol (79% for the two steps),³⁰ which was *O*-methylated by using $\text{Me}_3\text{O}^+ \text{BF}_4^-$ and Proton-Sponge[®] in CH_2Cl_2 (80% yield).



In summary, we have developed a highly stereoselective synthesis of the C(13)–C(25) fragment **1** of scytophycin C involving the aldol reaction of chiral methyl ketone **10** and the chiral aldehyde **3**, and have demonstrated that the stereoselectivity of the aldol reaction is dependent on the protecting group combinations chosen for the C(15)- and C(21)-alcohols. Further progress towards the completion of a synthesis of scytophycin C will be reported in due course.

Acknowledgements

Support provided by the National Institutes of Health (GM 38436) is gratefully acknowledged.

References

- Ishibashi, M.; Moore, R. E.; Patterson, G. M. L.; Xu, C.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5300.
- Moore, R.; Patterson, G.; Mynderse, J.; Barchi, J.; Norton, T.; Furusawa, E.; Furusawa, S. *Pure Appl. Chem.* **1986**, *58*, 263.
- Valeriote, F.; Moore, R. E.; Patterson, G. M. L.; Paul, V. J.; Scheuer, P. J.; Corbett, T. H. In *Anticancer Drug Discovery and Development: Natural Products and New Molecular Models*; Valeriote, F. A.; Corbett, T. H.; Baker, L. H., Eds.; Kluwer Acad. Publishers: Norwell, 1994; pp. 1–25.
- The C(1)–C(25) segments of scytophycin C and swinholide A are very similar structurally. Thus, synthetic studies on swinholide A and preswinholide are relevant to scytophycin C, and vice versa.
- Carmely, S.; Kashman, Y. *Tetrahedron Lett.* **1985**, *26*, 511.
- Kitagawa, I.; Kobayashi, M.; Katori, T.; Yamashita, M.; Doi, M.; Ishida, T.; Tanaka, J. *J. Am. Chem. Soc.* **1990**, *112*, 3710.
- Paterson, I.; Watson, C.; Yeung, K.-S.; Wallace, P. A.; Ward, R. A. *J. Org. Chem.* **1997**, *62*, 452.
- Paterson, I.; Yeung, K.-S.; Watson, C.; Ward, R. A.; Wallace, P. A. *Tetrahedron* **1998**, *54*, 11935.
- Paterson, I.; Watson, C.; Yeung, K.-S.; Ward, R. A.; Wallace, P. A. *Tetrahedron* **1998**, *54*, 11955.
- Grieco, P. A.; Speake, J. D. *Tetrahedron Lett.* **1998**, *39*, 1275.
- Grieco, P. A.; Speake, J. D.; Yeo, S. K.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 1125.

12. Paterson, I.; Yeung, K. S.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Lambole, S. *Tetrahedron* **1995**, *51*, 9467.
13. Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847.
14. A synthesis of preswinholide A has also been accomplished by Nakata and co-workers: Nagasawa, K.; Shimizu, I.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6885.
15. Gustin, D. J.; VanNieuwenhze, M. S.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 3443.
16. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
17. Roush, W. R.; Smith III, W. J., unpublished research results.
18. Kigoshi, H.; Suenaga, K.; Mutou, T.; Ishigaki, T.; Atsumi, T.; Ishiwata, H.; Sakakura, A.; Ogawa, T.; Ojika, M.; Yamada, K. *J. Org. Chem.* **1996**, *61*, 5326.
19. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 2815.
20. Aldol reactions of **2** with isobutyraldehyde gave 2:1 mixtures of diastereomeric aldols under both lithium (LHMDS, THF, -78°C) and titanium enolate conditions (TiCl_4 , *i*-Pr₂NEt, CH₂Cl₂, -78°C).
21. Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
22. Kozikowski, A. P.; Wu, J.-P. *Tetrahedron Lett.* **1987**, *28*, 5125.
23. Guindon, Y.; Yoakim, C.; Morton, H. E. *J. Org. Chem.* **1984**, *49*, 3912.
24. The 1,3-*cis* methylene acetal similarly prepared from the minor aldol diastereomer exhibited $J_{a,b}=11$ Hz and $J_{b,c}=9.5$ Hz.
25. Roush, W. R.; Bannister, T. D. *Tetrahedron Lett.* **1992**, *33*, 3587.
26. Roush, W. R.; Bannister, T. D.; Wendt, M. D. *Tetrahedron Lett.* **1993**, *34*, 8387.
27. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
28. The stereochemistry of aldols **19–23** was assigned by ¹H NMR correlations with **18**. In all cases, these assignments are fully consistent with assignments based on the analysis of the characteristic ABX pattern for the C(18)-CH₂ and C(19)-H resonances, as previously described (see ref. 15).
29. Evans, D. A.; Hoveyda, A. H. *J. Org. Chem.* **1990**, *55*, 5190, and references cited therein.
30. Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.