Pergamon

Tetrahedron Letters 40 (1999) 4955–4959

TETRAHEDRON LETTERS

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

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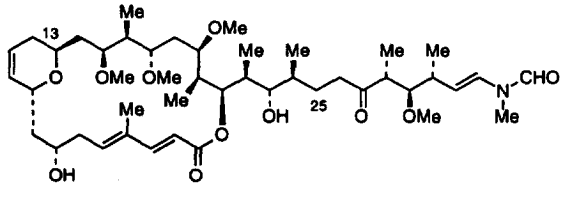
Received 5 April 1999; revised 26 April 1999; accepted 27 April 1999

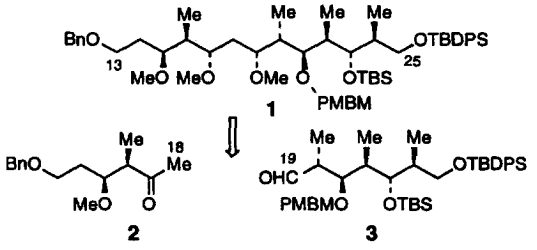
Abstract

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.

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 resemblance[4] 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]



scytophycin C



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

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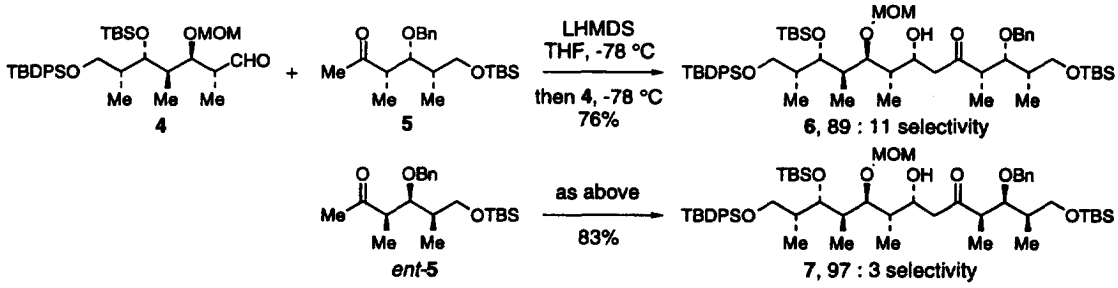
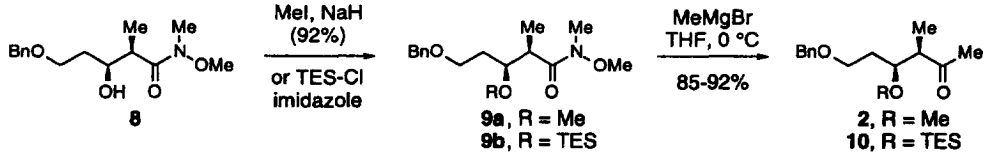
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00868-0

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.

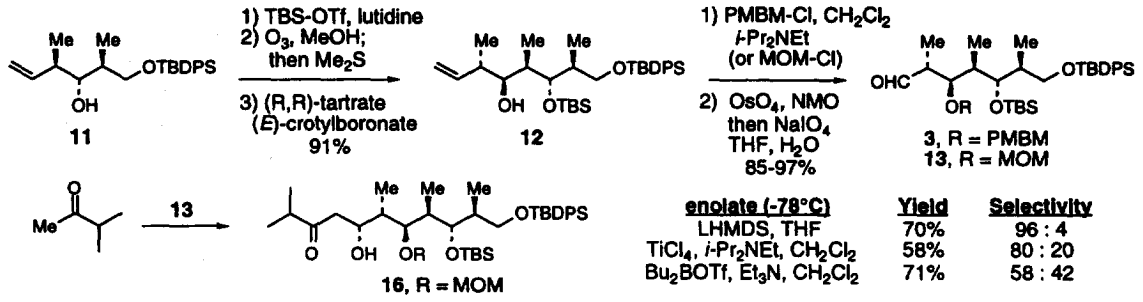


For example, in the (mismatched) aldol coupling of **4** and **5**, diastereomer **6** predominates with 89:11 selectivity.[15] On the other hand, when the lithium enolate of the enantiomeric methyl ketone, *ent*-**5**, is used, aldol **7** is the near exclusive product (97:3 ds).[17] Accordingly, we 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]

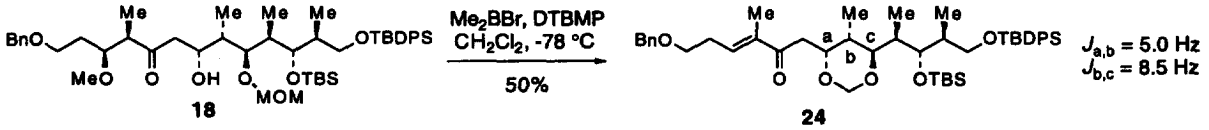


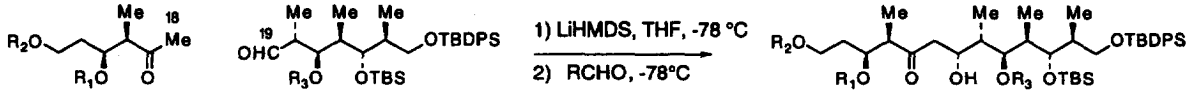
Aldehyde **3** was synthesized from the known homoallylic alcohol **11**.[21] Protection of the secondary hydroxyl group as a TBS ether followed by ozonolysis of the vinyl group gave an aldehyde that was subjected to standard diastereoselective crotylboration conditions,[21] thereby providing **12** 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.



enolate (-78°C)	Yield	Selectivity
LHMDS, THF	70%	96 : 4
$TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2	58%	80 : 20
Bu_2BOTf, Et_3N, CH_2Cl_2	71%	58 : 42

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 Me_2BBr in CH_2Cl_2 at –78°C in the presence of 2,6-di-*t*-butyl-4-methylpyridine (DTBMP).[23,24]

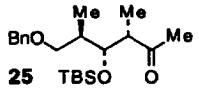




		Selectivity	Yield	
2, R_1 = Me, R_2 = Bn	**13**, R_3 = MOM	88 : 12	60%	**18**, R_1 = Me, R_2 = Bn, R_3 = MOM
2, R_1 = Me, R_2 = Bn	**13**, R_3 = MOM	91 : 09 †	–	**18**, R_1 = Me, R_2 = Bn, R_3 = MOM
2, R_1 = Me, R_2 = Bn	**13**, R_3 = MOM	80 : 20 **	60%	**18**, R_1 = Me, R_2 = Bn, R_3 = MOM
17, R_1 = Me, R_2 = TBS	**13**, R_3 = MOM	89 : 11	–	**19**, R_1 = Me, R_2 = TBS, R_3 = MOM
10, R_1 = TES, R_2 = Bn	**13**, R_3 = MOM	97 : 03	75%	**20**, R_1 = TES, R_2 = Bn, R_3 = MOM
10, R_1 = TES, R_2 = Bn	**14**, R_3 = PMB	78 : 22	74%	**21**, R_1 = TES, R_2 = Bn, R_3 = PMB
10, R_1 = TES, R_2 = Bn	**15**, R_3 = BOM	97 : 03	70%	**22**, R_1 = TES, R_2 = Bn, R_3 = BOM
10, R_1 = TES, R_2 = Bn	**3**, R_3 = PMBM	97 : 03	81%	**23**, R_1 = TES, R_2 = Bn, R_3 = PMBM

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

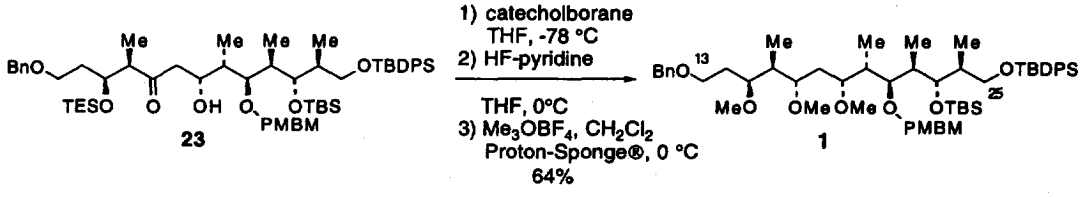
Because we had previously presented evidence that chelation of the δ-benzyl ether protecting group of **25** to the lithium ion reaction center plays a role in the aldol diastereoselectivity of this methyl ketone,[25,26] aldol reactions of **13** and the lithium enolate of **2** were performed in the 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 $Me_3O^+ BF_4^-$ 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.

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