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Studies Directed toward the Construction of the Polypropionate Fragment of Superstolide A

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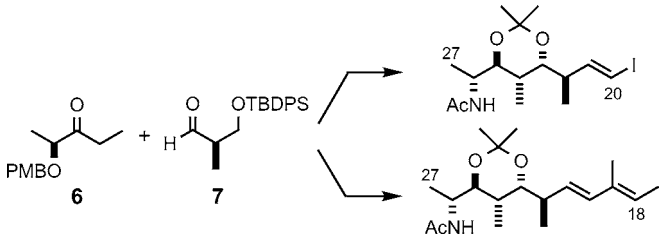
ABSTRACT



Highly stereoselective approaches directed toward the synthesis of the C18–C27 fragment of superstolide A are disclosed taking ketone 6 and aldehyde 7 as the only sources of chirality.

Superstolide A (**1**) is a macrolide isolated from the New Caledonian marine sponge *Neosiphonia superstes* that shows a remarkably potent cytotoxicity against several human and murine cancer cell lines.[1] Structurally, superstolide A is a 16-membered macrolactone composed of a densely functionalized *cis*-decalin core possessing two main appendages: (i) a fully conjugated C1−C7 triene ester and (ii) a polypropionate-like C18−C27 fragment (see Figure 1).[2] Its appealing biological activity and the synthetic challenge that such a structure represents have prompted several groups to address its synthesis.[3] However, no total synthesis has been reported so far.

In this context, we now describe highly stereoselective approaches toward the construction of the C18−C27 fragment based on the retrosynthetic analysis outlined in Scheme 1. Strategic disconnections of the ester linkage and the C19−C20 (palladium-mediated Suzuki or Stille cross-coupling) or C20−C21 (Julia−Kocienski olefination) bonds reveal vinyl iodide **2** and sulfone **3** as potential targets. In turn, both compounds could emerge from the single intermediate **4**, which would be prepared from β-hydroxy ketone **5** through a stereoselective anti reduction followed by standard functional group manipulations. Finally, we envisaged that **5** might be easily prepared by taking advantage of a recently reported substrate-controlled aldol reaction[4] from the chiral ketone **6** and aldehyde **7**. Therefore, the proper setting-up

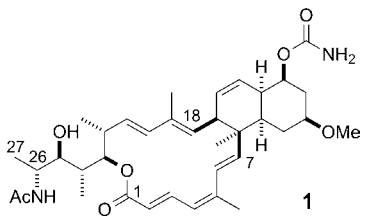


Figure 1. Superstolide A.

(1) D'Auria, M. V.; Debitus, C.; Gomez Paloma, L.; Minale, L.; Zampella, A. *J. Am. Chem. Soc.* **1994**, *116*, 6658.

(2) The numbering system proposed by Minale et al. (see ref 1) has been slightly modified to better clarify the syntethic strategy.

(3) (a) Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett.* **1996**, *37*, 8989. (b) Yu, W.; Zhang, Y.; Jin, Z. *Org. Lett.* **2001**, *3*, 1447. (c) Zampella, A.; D'Auria, M. V. *Tetrahedron*: *Asymmetry* **2001**, *12*, 1543. (d) Roush, W. R.; Hertel, L.; Schnaderbeck, M. J.; Yakelis, N. A. *Tetrahedron Lett.* **2002**, *43*, 4885. (e) Yakelis, N. A.; Roush, W. R. *J. Org. Chem.* **2003**, *68*, 3838.

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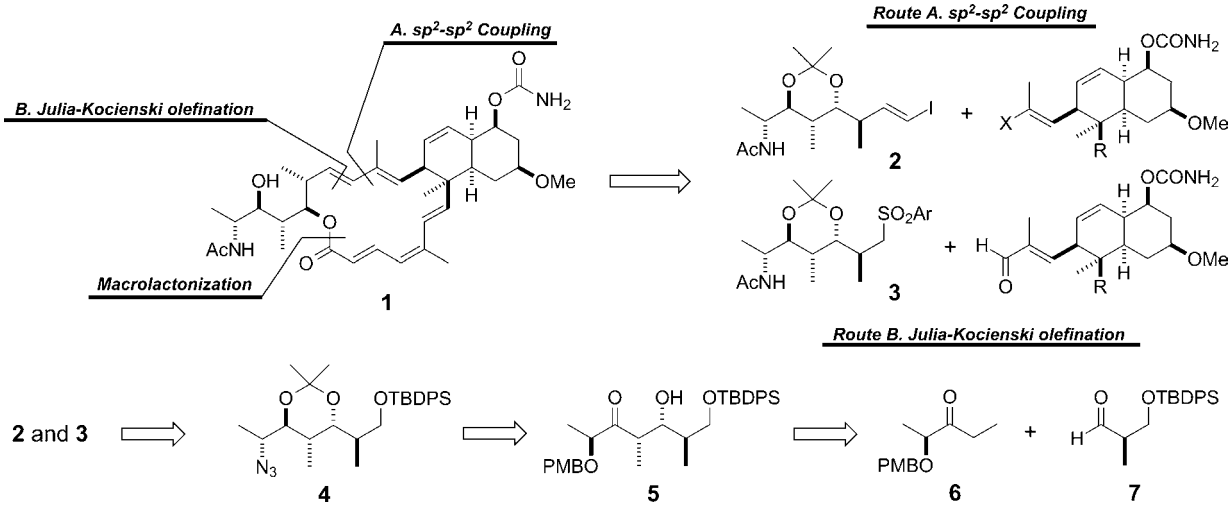
Scheme 1. Retrosynthetic Analysis of **1**



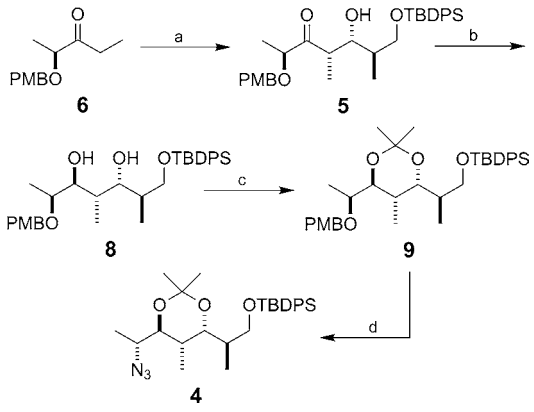
of all five stereocenters in **2** or **3** relies upon the configuration of **6** and **7**, without requiring other sources of chirality.

It also deserves to be mentioned that a single isopropylidene acetal was foreseen to protect the C23−C25 1,3-diol. This choice makes the synthesis more efficient but obviously jeopardizes the regioselective macrocyclic lactonization. Fortunately, it is well-known that such a process is only successful if the corresponding seco acid can reach a suitable conformation close to that of the final macrolactone.[5] This geometrical requirement can be anticipated through a careful analysis of the NMR data of both components and, more theoretically, by means of molecular modeling.[6] In our case, spectroscopic data reported by Minale et al.[1] display an excellent agreement between the ^{1}H and ^{13}C NMR spectra of **1** and its seco acid methyl ester. Additionally, molecular mechanics applied to the putative 18-membered macrolactone proves that a dramatic conformational change is associated with this new macrolide. Thus, it seems plausible to expect that final cyclization will take place regioselectively at C23 from the seco acid containing two available hydroxyl groups.[7]

Keeping in mind these ideas, we first proceeded to the synthesis of fully protected azido polyol **4** (see Scheme 2). Addition of the titanium enolate of ketone **6**[8] to aldehyde **7**[9] provided anti Felkin adduct **5** in 82% yield as a single diastereomer. This highly stereoselective titanium aldol reaction just requires 1.2 equiv of aldehyde **7** and is routinely performed in 0.5−5 mmol scale with similar results. Next, diastereomerically pure anti diol **8** was isolated in excellent yield (92%) after chromatographic purification of a 94:6 dr mixture of diols obtained by reduction of **5** with $(Me_4N)HB(OAc)_3$.[10] Diol **8** was then converted into the corresponding isopropylidene acetal **9** in 92% yield following standard procedures.[11] Finally, a three-step sequence based on a DDQ mediated deprotection of the OPMB group, mesylation of the resulting alcohol, and introduction of the azido group with NaN_3 through an S_N2 process readily afforded the desired azido polyol **4** in 80% overall yield without the need for purification of either intermediate.

Having found an expeditious and highly stereoselective route to the key intermediate **4**, we focused our attention on the synthesis of vinyl iodide **2** (see Scheme 3). Not

Scheme 2. Synthesis of Protected Azido Polyol **4**[a]



[a] Reaction conditions: (a) (i) (*i*-PrO)$TiCl_3$, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 1.5 h; (ii) **7**, −78 °C, 2 h; 82%. (b) $(Me_4N)HB(OAc)_3$, CH_3CN/AcOH 65:35, −40 to −25 °C, 12 h; 94:6 dr, 92%. (c) CH_2Cl_2/$Me_2C(OMe)_2$ 1:1, PPTS cat., rt, 24 h; 92%. (d) (i) DDQ, CH_2Cl_2/phosphate pH 7 10:1, 0 °C, 2 h; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 4 h; (iii) NaN_3, DMF, 70 °C, 2 h; 80%.

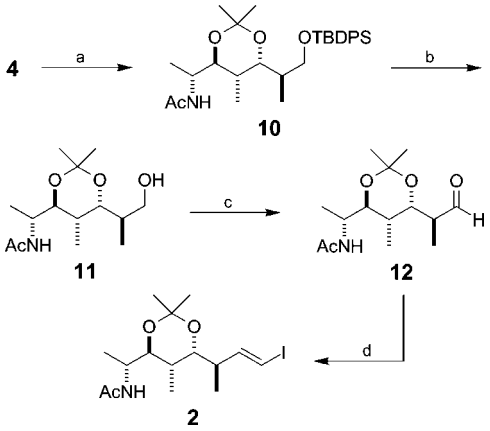
(4) Solsona, J. G.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519.

(5) (a) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613.

(6) (a) Matsushima, T.; Horita, K.; Nakajima, N.; Yonemitsu, O. *Tetrahedron Lett.* **1996**, *37*, 385. (b) White, J. D.; Blakemore, P. R.; Browder, C. C.; Hong, J.; Lincoln, C. M.; Nagornyy, P. A.; Robarge, L. A.; Wardrop, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 8593.

(7) For other related cyclizations, see: (a) Paterson, I.; Yeung, K.-S.; Ward, R. A.; Smith, J. D.; Cumming, J. G.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9467. (b) Evans, D. A.; Trotter, B. W.; Coleman, P. J.; Côté, B.; Dias, L. C.; Rajapakse, H. A.; Tyler, A. N. *Tetrahedron* **1999**, *55*, 8671. (c) Schuppan, J.; Wehlan, H.; Keiper, S.; Koert, U. *Angew. Chem., Int. Ed.* **2001**, *40*, 2063. (d) Hanessian, S.; Ma, J.; Wang, W. *J. Am. Chem. Soc.* **2001**, *123*, 10200. (e) Wender, P. A.; Hegde, S. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 4956.

Scheme 3. Synthesis of Vinyl Iodide **2**[a]

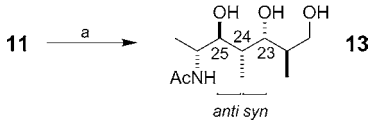


[a] Reaction conditions: (a) (i) Me_3P, H_2O, THF, rt, 12 h; (ii) Ac_2O, Et_3N, CH_2Cl_2, rt, 1 h; 88%. (b) TBAF·$3H_2O$, THF, rt, 30 h; 99%. (c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 1 h. (d) CHI_3, $CrCl_2$, THF, rt, 12 h; 95:5 *E*/*Z*, 61%.

surprisingly, Takai's olefination procedure[12] was expected to play a pivotal role in this transformation. Then, given that chromium(II) would easily reduce the azido group in **4**,[13] we first confronted its conversion into the required amide. Reduction of azides with Ph_3P (Staudinger reaction)[14] and subsequent hydrolysis of the corresponding phosphazenes constitutes one of the mildest and selective ways of access to primary amines.[15] This procedure generally provides the desired amine in quantitative yields, but use of Ph_3P requires high temperatures and chromatographic purification to remove the resulting $Ph_3P{=}O$. Having recognized that replacement of Ph_3P by more nucleophilic trialkylphosphines, particularly Me_3P, overcomes the above-mentioned drawbacks,[16,17] azido polyol **4** was easily reduced (Me_3P/H_2O) at room temperature and acylated (Ac_2O/Et_3N) into the acetamide derivative **10** in 88% yield. Removal of the silicon protecting group furnished primary alcohol **11** quantitatively. With use of Swern conditions, **11** was smoothly oxidized to aldehyde **12**, which was immediately submitted to the next reaction. Finally, the Takai olefination was performed with CHI_3 and $CrCl_2$ in THF, providing a 95:5 ratio of *E*/*Z* vinyl iodide **2** in 61% yield over two steps.[18]

(8) Ferreró, M.; Galobardes, M.; Martín, R.; Montes, T.; Romea, P.; Rovira, R.; Urpí, F.; Vilarrasa, J. *Synthesis* **2000**, 1608.
(9) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348.
(10) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
(11) Greene, T. W.; Wuts, R. G. M. In *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999.
(12) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(13) Bartra, M.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron* **1990**, *46*, 587.
(14) For a review on the Staudinger reaction and phosphazene chemistry, see: Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353.
(15) (a) Vaultier, M.; Knouzi, N.; Carrie, R. *Tetrahedron Lett.* **1983**, *24*, 763. (b) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297.
(16) (a) Ariza, X.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1999**, *40*, 7515. (b) Nyffeler, P. T.; Liang, C.-H.; Koeller, K. M.; Wong, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 10773. (c) For a review on trialkyl phosphines, see: Valentine, D. H.; Hillhouse, J. H. *Synthesis* **2003**, 317.

Scheme 4. Synthesis of Trihydroxy Acetamide **13**[a]

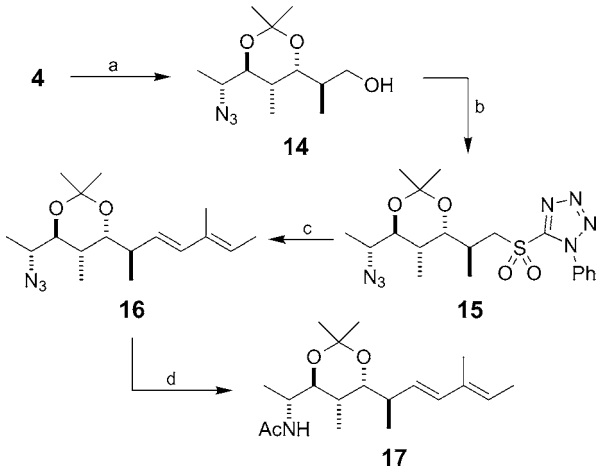


[a] Reaction conditions: (a) Amberlyst 15, CH_3OH, rt, 3 days; 80%.

Although the stereoselective reactions reported so far have proved to be highly reliable, we decided at this point to corroborate the configuration of the stereocenters embedded in **2**. Analysis of the ^1H and ^{13}C NMR spectra[19] of **9**−**12** and **2** proved the C24−C25 anti and C23−C24 syn relationships existing between these chiral centers (see Scheme 4). Additionally, experimental data for **13** previously reported[3c] gave us the opportunity to correlate our assignment. With this proposal, trihydroxy amido **13** was easily obtained from alcohol **11** in 80% yield after chromatographic purification. Even though the specific rotation of the compound prepared in this way, $[\alpha]_D$ +32.4 (*c* 0.85, CH_3OH), was exceptionally high,[20] the good agreement between its NMR spectroscopic data and those reported by D'Auria et al. confirms our stereochemical assignment.

Eventually, the synthesis of the key sulfone **3** (see Scheme 1) was addressed as envisaged. However, it was discovered after several unsuccessful attempts that a suitable functional group manipulation could give quick access to an alternative and more elaborated model for the C18−C27 appendage, as shown in Scheme 5. After removing the silicon protecting group of **4**, the new synthetic sequence began with the efficient preparation (84% yield) of the azido sulfone **15** through a Mitsunobu reaction followed by oxidation of the resulting thioether. With this advanced intermediate in hand,

Scheme 5. Synthesis of Acetamide **17**[a]



[a] Reaction conditions: (a) TBAF·$3H_2O$, THF, rt, 12 h; 91%. (b) (i) $Ph(CN_4)SH$, Ph_3P, DEAD, THF, rt, 4 h; (ii) $(NH_4)_2MoO_4$, H_2O_2, THF, rt, 24 h; 84%. (c) LHMDS, (*E*)-2-methyl-2-butenal, 1,2-dimethoxyethane, −65 °C to room temperature; 94:6 *EE*/*ZE*, 72%. (d) Me_3P, AcCl, benzene, rt, 5 h; 64%.

reduction of the azido group was delayed and a Julia−Kocienski[21] olefination involving tiglic aldehyde was carried out instead. The aforementioned process took place in a straightforward manner with LHMDS in 1,2-dimethoxyethane, being able to isolate azido diene **16** in 72% yield as a *E*,*E*/*Z*,*E* 94:6 mixture of dienes.[18] Finally, the azido group was converted into the corresponding acetamide **17** in a one-pot reaction.[22] The Staudinger reaction between azide **16** and Me_3P gives in 2 h at room temperature the corresponding phosphazene, which finally reacts with AcCl to afford, after hydrolysis, the amide **17** in 64% yield.

In summary, we have disclosed a novel and concise route to the stereoselective construction of the C18−C27 fragment of superstolide A. Our strategy highlights the synthetic potentiality of the titanium-mediated aldol reaction based on the chiral α-hydroxy ketone **6**, which gives access to valuable enantiopure intermediates under substrate control.

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Supporting Information Available: Experimental procedures, physical and spectroscopic data of **2**, **4**, **5**, **8**−**17**, and ^1H and ^{13}C NMR spectra of **2**, **4**, **5**, **13**, and **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Toluene solutions of Me_3P are commercially available. The resulting $Me_3P{=}O$ is water soluble and is easily removed by washing the organic layer.

(18) Diastereomeric ratio was established by 400-MHz ^1H NMR.

(19) Relative stereochemistry of 1,3-dioxane moieties has been assigned after $^3J(H-H)$ coupling constants analysis and NOESY experiments. Additionally, configurational assignment with the ^{13}C NMR acetonide diagnostic has been followed. For leading references, see: (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett.* **1990**, *31*, 945. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099. (c) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res.* **1998**, *31*, 9.

(20) The reported specific rotation is lower: $[\alpha]_D$ +3.4 (*c* 1, CH_3OH). See ref 3c.

(21) Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26.

(22) Bosch, I.; González, A.; Urpí, F.; Vilarrasa, J. *J. Org. Chem.* **1996**, *61*, 5638.