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Synthesis of the C(18)–C(26) segment of superstolide A

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Abstract—A stereoselective synthesis of the C(20)–C(26) fragment of superstolide A is described. © 2002 Elsevier Science Ltd. All rights reserved.

In 1994 Minale and co-workers reported the isolation and structure determination of superstolides A (**1**) and B (**2**), a pair of 16-membered macrolides, from the New Caledonian sponge *Neosiphonia superstes*. 1,2 These structurally novel macrolides are highly cytotoxic against cancer cell lines including murine P388 leukemia cells $(IC_{50} = 0.003 \mu g/mL$ for 1 and 2), human nasopharyngeal cells $(0.005 \mu g/mL$ for 2), and non-small-cell lung carcinoma cells $(IC_{50} = 0.04 \mu g/mL$ for 1 and 2), and as such are viewed as important targets for total synthesis.^{3–5} In

1996 we reported a highly stereoselective synthesis of the *cis*-fused octahydronaphthalene nucleus of **1** and **2** (cf. **4**) via the intramolecular Diels–Alder reaction of trienal **3**. ³ Of considerable interest in this sequence was the striking dependence of IMDA diastereoselectivity on the reaction solvent, with the best results being obtained in trifluoroethanol. $6-9$ Recent reports of syntheses of the $C(20)-C(26)$ fragment of superstolide A by Jin and D'Auria prompt us to report our synthesis of the C(18)–C(26) fragment at this time.^{4,5}

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Our current strategy for the synthesis of **1** calls for the key IMDA reaction to be performed at a late stage of the synthesis, ideally at the stage of macrocycle **5** after the major fragments are coupled. This approach would constitute an interesting application of the transannular Diels–Alder reaction¹⁰ in the ring contraction mode,¹¹ thereby facilitating construction of the highly unsaturated 16-membered ring of the natural product target and minimizing functional group incompatibility problems during the fragment assembly sequence.¹² We envisage that macrocycle **5** will be accessible from precursors **6** and **7**. Towards this goal, we report herein our first generation synthesis of the $C(18)-C(26)$ dienyl iodide fragment **7**.

ture. Accordingly, the desired diastereomer **11** was obtained in up to 67% yield and 87:13 d.s. from the alaninol intermediate. Fortunately, the two diastereomers could be separated by recrystallization of the mixture from ether/pentane, thereby providing pure **11** for use in the next transformations. Protection of **11** as the acetonide derivative **12** proceeded without complication. After ozonolytic cleavage of the vinyl group of **12**, the stage was set for a second crotylboration reaction, this time employing the (*S*,*S*)-enantiomer of the crotylboronate reagent **10**. The targeted 3,4-*anti*-4,5-*syn* diastereomer **14** was obtained, as expected,16 as the major product. However, we were surprised to find that the diastereoselectivity of this reaction was only

The synthesis of **7** originates from *N*-acetyl D-alanine methyl ester,¹³ which was reduced to the *N*-acetyl alaninol in 88% yield by using NaBH₄ and CaCl₂ in a 1:2 THF/ethanol co-solvent mixture.14 Oxidation of the alcohol using the standard Swern protocol¹⁵ then provided *N*-acetyl-D-alanine **9**. In order to avoid potential problems with racemization of the *N*-acetylamino aldehyde, intermediate **9** was used directly without purification in the subsequent diastereoselective (*E*)-crotylboration reaction using (R, R) -10.^{16,17} Owing to the poor solubility properties of **9**, it was necessary to perform this reaction in a 8:1 toluene/acetone co-solvent mix-

4:1, given our considerably greater success in utilizing this methodology in the synthesis of structurally complex polypropionate units.^{16–19} This result is reminiscent of earlier work that indicated that α - and β -alkoxy aldehydes often display diminished diastereoselectivity in allylboration reactions using the tartrate ester modified allylboronate reagents.²⁰ However, we had not previously experienced difficulties in the matched²¹ (E) crotylboration reactions of α -methyl- β -alkoxy aldehydes, which generally provide the 2,3-*anti*-4,5-*syn* product diastereomers (cf. the same stereochemistry as in **14**) with excellent stereoselectivity.¹⁶⁻¹⁹ The one dif-

ference between the aldehyde utilized here (**13**) compared to those in our previous synthetic efforts is that the B-alkoxy group is constrained with a cyclic protecting group, which enables the non-bonded lone pairs of electrons on the C(25)-oxygen atom to point towards the tartrate ester in the reaction transition state, a feature that we previously invoked as a reason for diminished diastereoselectivity in the allylboration reaction of α - and β -alkoxy aldehydes.²⁰ It is also perhaps worth noting that it is not obvious that Corey's explanation of the origin of asymmetric induction in the allylboration reactions of the tartrate ester modified allylboronates, involving formyl C-H···O hydrogen bonds, 22 is sufficient to rationalize the dependence of reaction diastereoselectivity (or enantioselectivity, for reactions with achiral aldehydes) on the reaction solvent, the presence (and directionality) of β -alkoxy groups, or the conformational rigidity of the tartrate auxiliary.20,23–25 Thus, we believe that our original dipole-based origin of asymmetric induction continues to merit consideration in the rationalization of the stereochemical course of these reactions.²⁶

Protection of the secondary hydroxyl group of **14** as a TBS ether proceeded uneventfully to provide the fully protected intermediate **15** in 92% yield. Ozonolysis of the vinyl group and application of the Takai olefination procedure then provided vinyl iodide **16** in 76% yield.27 Palladium(0) catalyzed cross coupling of **16** with the vinylzinc species generated by treatment of vinylstannane 17^{28} with BuLi in THF (-78° C) followed by addition of $ZnCl₂$ then provided the dienylic silane **18** in 62% yield.²⁹ Finally, treatment of the dienylsilane unit of **18** with NIS in EtCN at −50°C with warming to 0°C then provided the targeted dienylic iodide **7** in 87% yield.³⁰

In conclusion, a diastereoselective synthesis of dienylic iodide **7** is described. Further progress towards completion of the total synthesis of superstolide A will be reported in due course.

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References

- 1. D'Auria, M. V.; Debitus, C.; Paloma, L. G.; Minale, L.; Zampella, A. *J*. *Am*. *Chem*. *Soc*. **1994**, 116, 6658.
- 2. D'Auria, M. V.; Paloma, L. G.; Minale, L.; Zampella, A.; Debitus, C. *J*. *Nat*. *Prod*. **1994**, ⁵⁷, 1595.
- 3. Roush, W. R.; Champoux, J. A.; Peterson, B. C. *Tetrahedron Lett*. **1996**, 37, 8989.
- 4. Yu, W.; Zhang, Y.; Jin, Z. *Org*. *Lett*. **2001**, 3, 1447.
- 5. Zampella, A.; D'Auria, M. V. *Tetrahedron*: *Asymmetry* **2001**, 12, 1543.
- 6. Ciganek, E. *Org*. *React*. **1984**, 32, 1.
- 7. Craig, D. *Chem*. *Soc*. *Rev*. **1987**, 16, 187.
- 8. Fallis, A. G. *Can*. *J*. *Chem*. **1984**, 62, 183.
- 9. Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed. [4+2] Cycloadditions: intramolecular Diels– Alder reactions. Pergamon Press: Oxford, 1991; Vol. 5, pp. 513–550.
- 10. Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, ⁵⁷, 4243.
- 11. For an earlier demonstration of this strategy, see: Roush, W. R.; Koyama, K.; Curtin, M. L.; Moriarty, K. J. *J*. *Am*. *Chem*. *Soc*. **1996**, 118, 7502.
- 12. Elements of this strategy were used to great advantage in our total synthesis of chlorothricolide: Roush, W. R.; Sciotti, R. J. *J*. *Am*. *Chem*. *Soc*. **1998**, 120, 7411.
- 13. Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J*. *Am*. *Chem*. *Soc*. **1993**, 115, 10215.
- 14. Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J*. *Org*. *Chem*. **1987**, 52, 1487.
- 15. Tidwell, T. T. *Org*. *React*. **1990**, 39, 297.
- 16. Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J*. *Am*. *Chem*. *Soc*. **1990**, 112, 6339.
- 17. Roush, W. R.; Palkowitz, A. D.; Ando, K. *J*. *Am*. *Chem*. *Soc*. **1990**, 112, 6348.
- 18. Roush, W. R.; Palkowitz, A. D. *J*. *Org*. *Chem*. **1989**, 54, 3009.
- 19. Roush, W. R.; Brown, B. B. *J*. *Am*. *Chem*. *Soc*. **1993**, 115, 2268.
- 20. Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Straub, J. A.; Palkowitz, A. D. *J*. *Org*. *Chem*. **1990**, ⁵⁵, 4117.
- 21. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew*. *Chem*., *Int*. *Ed*. *Engl*. **1985**, ²⁴, 1.
- 22. Corey, E. J.; Lee, T. W. *Chem*. *Commun*. **2001**, 1359.
- 23. Roush, W. R.; Hoong, L. K.; Palmer, M. A. J.; Park, J. C. *J*. *Org*. *Chem*. **1990**, ⁵⁵, 4109.
- 24. Roush, W. R.; Banfi, L. *J*. *Am*. *Chem*. *Soc*. **1988**, 110, 3979.
- 25. Roush, W. R.; Grover, P. T. *J*. *Org*. *Chem*. **1995**, 60, 3806.
- 26. Roush, W. R.; Walts, A. E.; Hoong, L. K. *J*. *Am*. *Chem*. *Soc*. **1985**, 107, 8186.
- 27. Takai, K.; Nitta, K.; Utimoto, K. *J*. *Am*. *Chem*. *Soc*. **1986**, 108, 7408.
- 28. Nicolaou, K. C.; Piscopio, A. D.; Bertinato, P.; Chakraborty, T. K.; Minowa, N.; Koide, K. *Chem*. *Eur*. *J*. **1995**, 1, 318.
- 29. Pihko, P. M.; Koskinen, A. M. P. *Synlett* **1999**, 1966.
- 30. Stamos, D. P.; Taylor, A. G.; Kishi, Y. *Tetrahedron Lett*. **1996**, 37, 8647.