

Tetrahedron Letters 43 (2002) 4885-4887

TETRAHEDRON LETTERS

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

William R. Roush,* Larry Hertel, Matthew J. Schnaderbeck and Neal A. Yakelis

Department of Chemistry, University of Michigan, 930 North University, Ann Arbor, MI 48109-1055, USA Received 26 February 2002; accepted 25 April 2002

Abstract—A stereoselective synthesis of the C(20)–C(26) fragment of superstolide A is described. \bigcirc 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}



^{*} Corresponding author. E-mail: roush@umich.edu

^{0040-4039/02/\$ -} see front matter @ 2002 Elsevier Science Ltd. All rights reserved. PII: S0040-4039(02)00903-6

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 β -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.

Acknowledgements

This work was supported by a grant from the National Institutes of Health (GM 38436 to W.R.R). We also thank Eli Lilly for sabbatical support for L.H.

References

- D'Auria, M. V.; Debitus, C.; Paloma, L. G.; Minale, L.; Zampella, A. J. Am. Chem. Soc. 1994, 116, 6658.
- D'Auria, M. V.; Paloma, L. G.; Minale, L.; Zampella, A.; Debitus, C. J. Nat. Prod. 1994, 57, 1595.

- 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.
- 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.
- Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* 2001, 57, 4243.
- 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.
- 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.
- Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. J. Am. Chem. Soc. 1993, 115, 10215.
- 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.
- Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. J. Am. Chem. Soc. 1990, 112, 6339.
- Roush, W. R.; Palkowitz, A. D.; Ando, K. J. Am. Chem. Soc. 1990, 112, 6348.
- 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.
- 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.
- 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.
- Roush, W. R.; Walts, A. E.; Hoong, L. K. J. Am. Chem. Soc. 1985, 107, 8186.
- Takai, K.; Nitta, K.; Utimoto, K. J. Am. Chem. Soc. 1986, 108, 7408.
- 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.
- Stamos, D. P.; Taylor, A. G.; Kishi, Y. Tetrahedron Lett. 1996, 37, 8647.