



Tetrahedron Letters 44 (2003) 3915-3918

TETRAHEDRON LETTERS

Evaluation of asymmetric Diels–Alder approaches for the synthesis of the cyclohexene subunit of CP-225,917 and CP-263,114 $\stackrel{\star}{\sim}$

Alan Armstrong,* Nicholas G. M. Davies, Nathaniel G. Martin and Alistair P. Rutherford

Department of Chemistry, Imperial College London, South Kensington, London SW7 2AZ, UK

Received 27 February 2003; revised 20 March 2003; accepted 28 March 2003

Abstract—Asymmetric synthesis of a functionalised cyclohexenone required for total synthesis of CP-225,917 and CP-263,114 is reported, using a Lewis acid-promoted Diels–Alder reaction between a 2-silyloxy-1,3-diene and a dienophile bearing an oxazolidinone auxiliary. A novel method for appendage of the exocyclic malonate unit, via cyclopropane ring opening, is also described. © 2003 Elsevier Science Ltd. All rights reserved.

Challenging structures along with important biological activity (inhibition of *ras*-farnesyl protein transferase and squalene synthase) have made the natural products CP-225,917 1^{1} and the closely related CP-263,114 highly popular targets for total synthesis.^{2–4} We have previously reported a concise synthesis of a model bicyclo[4.3.1]octenone core 2 involving reaction of the cyclohexenone **3a** ($R^{1}=R^{2}=H$) with a bis-electrophile equivalent,^{5a,b} as well as methodology for the construc-

tion of the γ -lactone acetal unit.^{5c} Another important requirement for extension of our strategy to a total synthesis is a route to enantiomerically pure cyclohexenone **3** bearing the C-9 and C-17 side-chains.[†] Diels–Alder chemistry was an obvious possibility, and we envisaged preparation of a silyl enol ether derivative **4** using this approach, by reaction of a dienophile **5** bearing a chiral auxiliary (e.g. Oppolzer sultam or Evans oxazolidinone) with suitable oxygenated dienes.



Scheme 1.

0040-4039/03/\$ - see front matter @ 2003 Elsevier Science Ltd. All rights reserved. doi:10.1016/S0040-4039(03)00835-9

Keywords: CP-compounds; Diels-Alder; oxazolidinone; cyclopropanation.

 $[\]pm$ Supplementary data associated with this article can be found at doi:10.1016/S0040-4039(03)00835-9

^{*} Corresponding author. Fax: +44-(0)20-7594-5804; e-mail: a.armstrong@imperial.ac.uk

[†] Natural product numbering as depicted in Scheme 1 is used throughout this paper.

Use of a 2-silyloxydiene **6** would lead to **4** directly, whilst use of Danishefsky's diene **8** would also afford **4** after conjugate reduction of the resulting enone **7**. Surprisingly, there appeared to be little literature precedent for the reaction of oxygenated dienes with chiral dienophiles of this type.^{6,7} Here we report an evaluation of several such Diels–Alder reactions and their application to the successful synthesis of **3**.⁸

Results and discussion

Our initial studies focused on Diels–Alder reactions of the more reactive bis-oxygenated diene **8** with chiral dienophiles⁹ **9a** and **10a** bearing the well-established Evans oxazolidinone and Oppolzer sultam auxiliaries. Perhaps not surprisingly, attempts to catalyze this reaction with Lewis acids were not productive, leading to polymerisation of electron-rich diene **8**. Turning to thermal conditions, reaction between Evans dienophile **10a** and diene **8** under sealed tube conditions followed by treatment with TMSOTf¹⁰ provided a mixture of four inseparable enones in a 50:30:18:7 ratio, suggesting poor cycloaddition regioselectivity and/or stereospecificity as well as stereoselectivity. However, reaction of diene **8** with Oppolzer dienophile **9a** under similar conditions gave a 9:1 mixture of enones. X-Ray



Scheme 2. Reagents and conditions: (a) (i) heat, toluene, sealed tube. For 11a: 150°C, 68 h; for 11b, 140°C, 21 h. (ii) TMSOTf, acetone, collidine, CH_2Cl_2 , -78°C; 75% for 11a, 59% for 11b.

crystallography¹¹ was used to assign the stereochemistry of the major isomer **11a** unambiguously (Scheme 2). This stereochemical outcome is in accord with the model proposed by Pindur in the Diels–Alder reaction of similar dienophiles with vinyl indoles.¹² Adduct **11a** has the opposite absolute configuration to that required for synthesis of **1**, but the other enantiomer of the chiral auxiliary is available. In order to incorporate functionality that could be used for conversion to the full natural product side-chain, a similar Diels–Alder sequence was carried out using the dienophile **9b**. This reaction afforded a 22:1 mixture of diastereomers according to LCMS analysis, with **11b** assumed to be the major by analogy to the formation of **11a**.

While the levels of stereocontrol achieved in the synthesis of **11b** were encouraging, attempts to effect conjugate reduction of the enone were not. Use of Wilkinson's catalyst in the presence of silanes did afford the desired products (cf. 4), but the reactions were unreliable, with varying amounts of ketone sideproducts obtained due to silvl enol ether hydrolysis. This led us to refocus our efforts on Diels-Alder reactions of monoxygenated dienes, which would provide a more direct route. Thermal reaction of 6 with 9b or 10b was slow, and appeared to proceed with poor levels of stereocontrol. Attempts to accelerate the reaction between 9b and 6 with Lewis acids (TiCl₄, Et₂AlCl or EtAlCl₂) led to decomposition of the diene. However, far more encouraging results were obtained with the oxazolidinone dienophiles 10b and 10c, which cleanly underwent the desired cycloaddition with 6 in the presence of 1.4 equiv. Et₂AlCl (Scheme 3). While the use of oxazolidinone dienophiles of this type in Diels-Alder reactions mediated by Et₂AlCl is well precedented for simple dienes,¹³ to the best of our knowledge this is the first example of the use of 2-silyloxydienes in this process. Careful control of reaction pH was necessary during work-up to prevent hydrolysis of the product silyl enol ether 12. ¹H NMR analysis indicated that the products 12 were obtained in good diastereoselectivity (89% de for 12a; 85% de for 12b); the diastereomers could be separated by flash chromatography, affording diastereomerically pure 12a (77% yield) or 12b (81%).¹⁴ Reductive removal of the auxiliary from 12b and benzyl protection led to 13. An efficient asymmetric route to a cyclohexene derivative with differential protection on the two side-chains had therefore been achieved.



Scheme 3. Reagents and conditions: (a) Et_2AlCl (1.4 equiv.), CH_2Cl_2 , -78 to -20°C, quenched with 9:1 NH₃ (aq):NH₄Cl (aq), 77% for **12a**, 81% for **12b**. (b) LiBH₄ (1.05 equiv.), EtOH (1 equiv.), THF, 0°C to rt, 51%. (c) NaH, THF, then BnBr, "Bu₄NBr (cat.), 60% (73% based on recovered starting material).



Scheme 4. Reagents and conditions: (a) TiCl₄, diethyl ketomalonate, -78° C, 30 min, then add 13, THF, 51%. (b) 2 mol% Cu(acac)₂, 1.1 equiv. EtO₂CCHN₂, EtOAc, 110°C, 96%. (c) (i) LDA, THF, -78° C, 30 min; (ii) add EtO₂CCl, warm to rt, 12 h; (iii) 0.5 equiv. 1 M TBAF, THF, 73%. (d) NaHMDS, NBS, 92%. (e) DABCO[®], C₆H₆, 92%.

Reaction of 13 with diethyl ketomalonate in the presence of TiCl₄ allowed installation of the diester unit in 14 (Scheme 4). In our model synthesis lacking the side-chains,^{5a,b} we were able to effect elimination of the tertiary hydroxyl and olefin migration by conversion to the acetate with TMSOTf/Ac₂O followed by reaction with DABCO. However, attempts to functionalise the tertiary hydroxyl in 14 were thwarted by competing deprotection of the PMB-ether and cyclisation of the resulting hydroxyl onto the ketone group. Similar difficulties were encountered with TBDMS-protection in place of PMB. These problems required us to develop a new method for incorporation of the malonate carbon atoms, inspired by Reissig's donor-acceptor-substituted cyclopropane chemistry.¹⁵ Thus, Cu-catalysed cyclopropanation of 13 with ethyl diazoacetate led to 15. Deprotonation and reaction with ethyl chloroformate followed by treatment with fluoride resulted in opening of the cyclopropane ring, providing 16. The cyclohexenone double bond could then be introduced by bromination/elimination accompanied by spontaneous alkene migration, affording the desired cyclohexene $3b^{16}$ with differentially protected sidechains.

In conclusion, we have examined the Diels–Alder reactions of monooxygenated diene 6 and bisoxygenated diene 8 with dienophiles 9 and 10. Bisoxygenated diene 8 reacts under thermal (sealed tube) conditions with sultam dienophiles 9 with good diastereoselectivity. For monooxygenated diene 6, best results were obtained in an Et₂AlCl-mediated cycloaddition with the oxazolidinones 10. We have also demonstrated a novel method for the appendage of a malonate unit to a silyl enol ether, via cyclopropanation/ring opening. In addition to the application to our ongoing synthetic studies on the CP-compounds, these results may have more general application to the asymmetric synthesis of functionalised cyclohexene derivatives.

Acknowledgements

We thank the EPSRC (GR/M25438) for funding this work. We are also grateful to Pfizer, AstraZeneca, Merck Sharp and Dohme and Bristol-Myers Squibb for generous unrestricted funding of our research programme.

References

- (a) Dabrah, T. T.; Harwood, H. J.; Huang, L. H.; Jankovich, N. D.; Kaneko, T.; Li, J. C.; Lindsey, S.; Moshier, P. M.; Subashi, T. A.; Therrien, M.; Watts, P. C. J. Antibiot. 1997, 50, 1–7; (b) Dabrah, T. T.; Kaneko, T.; Massefski, W.; Whipple, E. B. J. Am. Chem. Soc. 1997, 119, 1594–1598.
- For reviews, see: (a) Hepworth, D. Chem. Ind. 2000, 59–65; (b) Starr, J. T.; Carreira, E. M. Angew. Chem., Int. Ed. 2000, 39, 1415–1421.
- For total syntheses, see: (a) Nicolaou, K. C.; Baran, P. S. Angew. Chem., Int. Ed. 2002, 41, 2679–2720; Nicolaou, K. C.; Jung, J.; Yoon, W. H.; Fong, K. C.; Choi, H.-S.; He, Y.; Zhong, Y.-L.; Baran, P. S. J. Am. Chem. Soc. 2002, 124, 2183–2189; Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Fong, K. C.; Choi, H.-S. J. Am. Chem. Soc. 2002, 124, 2190–2201; Nicolaou, K. C.; Zhong, Y.-L.; Baran, P. S.; Jung, J.; Choi, H.-S.; Yoon, W. H. J. Am. Chem. Soc. 2002, 124, 2202–2211; (b) Tan, Q.; Danishefsky, S. J. Angew. Chem., Int. Ed. 2000, 39, 4509–4511; (c) Chen, C.; Layton, M. E.; Sheehan, S. M.; Shair, M. D. J. Am. Chem. Soc. 2000, 122, 7424–7425; (d) Waizumi, N.; Itoh, T.; Fukuyama, T. J. Am. Chem. Soc. 2000, 122, 7825–7826.
- For recent model studies, see papers cited in Refs. 5a and 5c and also: (a) Spiegel, D. A.; Wood, J. L. *Tetrahedron* 2002, 58, 6545–6554; Mehta, G.; Kumaran, R. S. *Chem. Commun.* 2002, 1456–1457; Chen, L.; Zhang, Z. Q.; Schultz, A. *Tetrahedron Lett.* 2002, 43, 4711–4715; Clive, D. L. J.; Ou, L. *Tetrahedron Lett.* 2002, 43, 4559–4563; Ohmori, N. J. Chem. Soc., Perkin Trans. 1 2002, 755–

767; Sulikowski, G. A.; Agnelli, F.; Spencer, P.; Koomen, J. M.; Russell, D. H. Org. Lett. 2002, 4, 1447–1450;
Sulikowski, G. A.; Liu, W. D.; Agnelli, F.; Corbett, R. M.; Luo, Z.; Hershberger, S. J. Org. Lett. 2002, 4, 1451–1454.

- (a) Armstrong, A.; Critchley, T. J.; Gourdel-Martin, M.-E.; Kelsey, R. D.; Mortlock, A. A. J. Chem. Soc., Perkin Trans. 1 2002, 1344–1350; (b) Armstrong, A.; Critchley, T. J.; Mortlock, A. A. Synlett 1998, 552–553; (c) Armstrong, A.; Critchley, T. J.; Gourdel-Martin, M.-E.; Kelsey, R. D.; Mortlock, A. A. Tetrahedron Lett. 2002, 43, 6027–6030.
- 6. Of the scattered examples in the literature, most employ α -methacrylate-derived dienophiles. Boeckman has reported asymmetric Diels-Alder reactions of methacrylate dienophiles bearing a camphor-derived lactam, but low selectivities were obtained with simple 2-silyloxy-1,3dienes. See: Boeckman, R. K., Jr.; Laci, M.; Johnson, A. T. Tetrahedron: Asymmetry 2001, 12, 205-217; Boeckman, R. K., Jr.; Liu, Y. J. Org. Chem. 1996, 61, 7984-7985; Boeckman, R. K., Jr.; Nelson, S. G.; Gaul, M. D. J. Am. Chem. Soc. 1992, 114, 2258-2260. For reaction of a sultam-bearing α -methacrylate dienophile with a 2-silyloxy-1,3-diene, see: Oppolzer, W.; Seletsky, B. M.; Bernardinelli, G. Tetrahedron Lett. 1994, 35, 3509-3512. For dimethyl fumarate with 2-trimethylsilyloxy-1,3-butadiene, see: Furata, K.; Iwanga, K.; Yamamoto, H. Tetrahedron Lett. 1986, 27, 4507-4510.
- 7. An alternative approach, which we have not explored, would employ Rawal's chiral 1-amino-3-silyloxy-1,3-dienes. To the best of our knowledge, however, these have not been used with β -alkyl-substituted acrylates. See: (a) Janey, J. M.; Iwama, T.; Kozmin, S. A.; Rawal, V. H. J. Org. Chem. 2000, 65, 9059–9068; (b) Kozmin, S. A.; Rawal, V. H. J. Am. Chem. Soc. 1999, 121, 9562–9573.
- For an alternative approach to chiral 4,5-disubstituted cyclohex-2-enones, see: Quattropani, A.; Anderson, G.; Bernardinelli, G.; Kundig, E. P. J. Am. Chem. Soc. 1997, 119, 4773–4774.
- The dienophiles were prepared by reaction of the appropriate aldehyde RCHO with the auxiliary-bearing diethyl phosphonate. For sultam dienophiles, see: (a) Oppolzer, W.; Dupuis, D.; Poli, G.; Raynham, T. M.; Bernardinelli, G. *Tetrahedron Lett.* 1988, 29, 5885–5888. For oxazolidinones, see: (b) Ishizaki, M.; Hara, Y.; Kojima, S.; Hoshino, O. *Heterocycles* 1999, 50, 779–790; (c) Katsumata, A.; Iwaki, T.; Fukumoto, K.; Ihara, M. *Heterocycles* 1997, 46; 605–616.
- 10. Vorndam, P. E. J. Org. Chem. 1990, 55, 3693-3695.
- 11. We thank Dr. A. J. Blake, Dept. of Chemistry, University of Nottingham for this structure determination. Crystallographic data (excluding structure factors) for **11a**

have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 204443. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

- Pindur, U.; Lutz, G.; Fischer, G.; Schollmeyer, G.; Massa, W.; Schroder, L. *Tetrahedron* **1993**, *49*, 2863– 2872.
- Evans, D. A.; Chapman, K. T.; Bisaha, J. J. Am. Chem. Soc. 1988, 110, 1238–1256.
- 14. The stereochemical outcome of this reaction was assigned based on the Evans chelation model for Diels-Alder reactions of this type of dienophile with simple dienes (Ref. 13). This was confirmed by correlation of sign of optical rotation to compounds obtained by manipulation of 11b. Details will be reported in a full account of this work. The crystal structure of the Diels-Alder adduct between 10a and 2-methoxy-1,3-butadiene has been reported previously, without details of the conditions used for the cycloaddition. The stereochemistry of this compound is consistent with that in Scheme 3. See: Marsh, R. E.; Schaefer, W. P.; Kukkola, P. J.; Myers, A. G. Acta Crystallogr. 1992, C48, 1622–1644.
- (a) Kahn, F. A.; Czerwonka, R.; Reissig, H.-U. *Eur. J.* Org. Chem. 2000, 3607–3617; (b) Reissig, H.-U. Top. Curr. Chem. 1998, 144, 73–135; (c) Kunkel, E.; Reichelt, I.; Reissig, H.-U. Liebigs Ann. Chem. 1984, 512–530; (d) Reichelt, I.; Reissig, H.-U. Liebigs Ann. Chem. 1984, 531–551; (e) Reissig, H.-U.; Reichelt, I.; Kunz, T. Org. Synth. Coll. Vol. 9, 573; (f) Reissig, H.-U.; Zimmer, R. Chem. Rev. 2003, 103, 1151–1196.
- 16. Data for **3b**: colourless oil; $[\alpha]_{D}^{21} = +69.0$ (c 0.58 CHCl₃); v_{max} 2918, 2856, 1748, 1733, 1677, 1614, 1513, 1456, 1303, 1247, 1097, 1033 cm⁻¹; $\delta_{\rm H}$ (250 MHz, CDCl₃): 7.38–7.25 (5H, m), 7.23 (2H, d, J=8.9 Hz), 6.98 (1H, dd, J=3.2, 0.8 Hz, CH=CCO), 6.85 (2H, d, J=8.9 Hz), 4.69 (1H, s, CH(CO₂Et)₂), 4.51 (2H, s), 4.39 (2H, s), 4.12–4.25 (4H, m, OC H_2 CH₃), 3.79 (3H, s, OC H_3), 3.66 (1H, dd, J=9.3, 5.0 Hz, CH₂OBn), 3.38–3.57 (3H, m, CH₂OBn, CH2OPMB), 2.58-2.71 (2H, m), 2.21-2.38 (2H, m), 1.88 (1H, m, CHCH₂OBn), 1.60 (1H, m, CH(CH₂)₂OPMB), 1.24 (3H, t, J=7.2 Hz, OCH₂CH₃), 1.22 (3H, t, J=7.2Hz, OCH₂CH₃); δ_C (62.5 MHz, CDCl₃): 196.5 (C), 167.9 (C), 167.8 (C), 159.2 (C), 149.7 (C), 138.0 (C), 132.6 (C), 130.3 (C), 129.2 (CH), 128.4 (CH), 127.7 (CH), 127.5 (CH), 113.8 (CH), 73.2 (CH₂), 72.7 (CH₂), 70.4 (CH₂), 67.1 (CH₂), 61.7 (CH₂), 55.3 (CH₃), 50.5 (CH), 42.4 (CH), 41.3 (CH₂), 33.2 (CH), 32.9 (CH₂), 14.0 (CH₃). m/z (CI): 556 (M+NH₄⁺, 2%), 538 (M⁺, 2%), 121 (100%). Found: $M+NH_4^+$, 556.2912. $C_{31}H_{42}NO_8$ requires: 556.2910.