Asymmetric Pauson–Khand Cyclization: A Formal Total Synthesis of Natural Brefeldin A†

Vania Bernardes,‡ Nina Kann,‡ Antoni Riera, Albert Moyano,§ Miquel A. Pericàs,§ and Andrew E. Greene*,‡

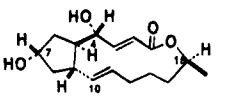
Chimie Recherches, LEDSS 3, Université J. Fourier, BP 53X, 38041 Grenoble, France, and Quimica Organica, Universitat de Barcelona, Marti i Franques 1-11, 08028 Barcelona, Spain

Received August 8, 1995

The usefulness of the Pauson–Khand reaction in racemic synthesis has been amply demonstrated. This cobalt-mediated uniting of an olefin, an acetylene, and carbon monoxide to yield a cyclopentenone has been applied on several occasions intramolecularly, as well as intermolecularly, for the racemic preparation of monocyclic, bicyclic, tricyclic, and tetracyclic natural products and derivatives.[1]

Examples of the use of this methodology for enantioselective synthesis, though, are scarce. We have recently shown[2] that the intramolecular Pauson–Khand bicyclization reaction can be effected asymmetrically and have used this version in an enantioselective approach to (+)-hirsutene.[2a] Although a greater challenge, the corresponding intermolecular asymmetric Pauson–Khand reaction has also been developed recently in our laboratories.[3] In this paper, we report the first application of this novel chemistry for a highly enantioselective formal total synthesis of the fungal metabolite (+)-brefeldin A (**1**).[4]

Brefeldin A has been, since its isolation and elucidation many years ago, a molecule of considerable interest to chemists, biologists, and pharmacologists because of its

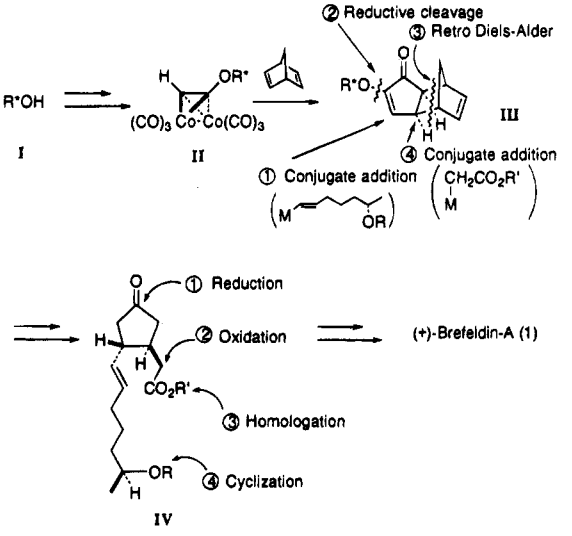


(+)-Brefeldin A (1)

well-functionalized macrolide structure and antitumor, antiviral, and antifungal effects.[5] Recently, however, with the reports from the NIH of its unique immunosuppressive properties, interest has soared.[6]

Our chiral auxiliary-based asymmetric Pauson–Khand route to this natural product, abridged in Scheme 1, was

Scheme 1



designed so as to merge with a previous synthesis at a key intermediate (IV, R = OTBDMS, R′ = n-C_4H_9).[5] In this approach, it was envisioned that the tricyclic enone III, synthesized by reaction of a chiral dicobalt hexacarbonyl–alkyne complex II with norbornadiene, would serve as a chiral cyclopentadienone equivalent[7] for the preparation of the key intermediate IV through the indicated transformations. The complex II would be prepared from a chiral alcohol I.

Two enantiopure alcohols, (1*S*,2*R*)-(+)-2-phenylcyclohexanol and (1*R*,2*S*,4*S*)-(+)-10-(methylthio)isoborneol, have been examined. Using our recently published procedures, each could be easily converted in 62% yield

* Tel: (33) 76-51-46-86; FAX: (33) 76-51-43-82; E-mail: Andrew.Greene@ujf-grenoble.fr.

† This paper is dedicated to Prof. James A. Marshall on the occasion of his 60th birthday.

‡ Université J. Fourier.

§ Universitat de Barcelona.

(1) For reviews, see: Pauson, P. L.; Khand, I. U. *Ann. N. Y. Acad. Sci.* **1977**, *295*, 2–14. Pauson, P. L. *Tetrahedron* **1985**, *41*, 5855–5860. Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081–1119. Schore, N. E. *Org. React.* **1991**, *40*, 1–90. Schore, N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp 1037–1064. For recent synthetic work, see: Rowley, E. G.; Shore, N. E. *J. Org. Chem.* **1992**, *57*, 6853–6861. Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169–170. van der Waals, A.; Keese, R. *Ibid.* **1992**, 570–571. Yoo, S.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968–6972. Naz, N.; Al-Tel, T. H.; Al-Abed, Y.; Voelter, W. *Ibid.* **1994**, *35*, 8581–8582. Johnstone, C.; Kerr, W. J.; Lange, U. *J. Chem. Soc., Chem. Commun.* **1995**, 457–458. Veretenov, A. L.; Koltun, D. O.; Smit, W. A.; Strelenko, Y. A. *Tetrahedron Lett.* **1995**, *36*, 4651–4654.

(2) (a) Castro, J.; Sörensen, H.; Riera, A.; Morin, C.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *J. Am. Chem. Soc.* **1990**, *112*, 9388–9389. (b) Poch, M.; Valenti, E.; Moyano, A.; Pericàs, M. A.; Castro, J.; De Nicola, A.; Greene, A. E. *Tetrahedron Lett.* **1990**, *31*, 7505–7508. (c) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E.; Piniella, J.; Alvarez-Larena, A. *J. Organomet. Chem.* **1992**, *433*, 305–310. (d) Castro, J.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E. *Tetrahedron: Asymmetry* **1994**, *5*, 307–310. For a different approach, see: Stolle, A.; Becker, H.; Salaün, J.; de Meijere, A. *Tetrahedron Lett.* **1994**, *31*, 5521–3525.

(3) (a) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Bernardes, V.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. *J. Am. Chem. Soc.* **1994**, *116*, 2153–2154. (b) Bernardes, V.; Verdaguer, X.; Kardos, N.; Riera, A.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *Tetrahedron: Lett.* **1994**, *35*, 575–578. For another approach, see: Bladon, P.; Pauson, P. L.; Brunner, H.; Eder, R. *J. Organomet. Chem.* **1988**, *355*, 449–454. Brunner, H; Niedernhuber, A. *Tetrahedron: Asymmetry* **1990**, *1*, 711–714.

(4) For synthetic work through 1986, see: Montforts, F.-P.; Ockenfeld, M.; Rehm, D. In *Synform*; Quinkert, G., Eds.;VCH Verlagsgesellschaft: Weinheim, 1986; Vol. 4, pp 40–58. For recent syntheses, see: Corey, E. J.; Carpino, P. *Tetrahedron Lett.* **1990**, *31*, 7555–7558. Hatakeyama, S.; Sugawara, K.; Kawamura, M.; Takano, S. *Synlett* **1990**, 691–693. Taber, D.; Silverberg, L. J.; Robinson, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6639–6645. Solladié, G.; Lohse, O. *J. Org. Chem.* **1993**, *58*, 4555–4563. Miyaoka, H.; Kajiwara, M. *J. Chem. Soc., Chem. Commun.* **1994**, 483–484. Casy, G.; Gorins, G.; McCague, R.; Olivo, H. F.; Roberts, S. M. *Ibid.* **1994**, 1085–1086. Carnell, A. J.; Casy, G.; Gorins, G.; Kompany-Saeid, A.; McCague, R.; Olivo, H. F.; Roberts, S. M.; Willetts, A. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3431–3439. Kim, D.; Lim, J. I. *Tetrahedron Lett.* **1995**, *36*, 5035–5036.

(5) For our earlier synthetic work on brefeldin A and references to its isolation, elucidation, and these biological effects, see: Le Drian, C.; Greene, A. E. *J. Am. Chem. Soc.* **1982**, *104*, 5473–5483.

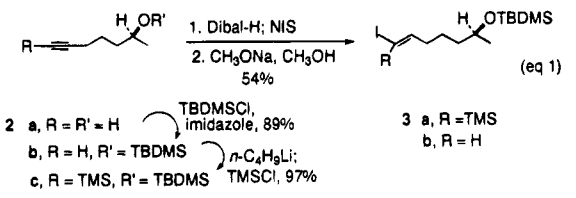
(6) Nuchtern, J. G.; Bonifacino, J. S.; Biddison, W. E.; Klausner, R. D. *Nature* **1989**, *339*, 223–226. For reviews, see: Klausner, R. D.; Donaldson, J. G.; Lippincott-Schwartz, J. *J. Cell. Biol.* **1992**, *116*, 1071–1080. *Chem. Eng. News* **1992**, *70*(43), 22–32.

(7) Cf. Schore, N. E. *Synth. Commun.* **1979**, *9*, 41–47. Toda, F.; Tanaka, K.; Marks, D.; Goldberg, I. *J. Org. Chem.* **1991**, *56*, 7332–7335. Takano, S.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Synlett* **1991**, 636–638. Dols, P. P. M. A.; Lacroix, L.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 3739–3742. Childs, B. J.; Edwards, G. L. *Ibid.* **1993**, *33*, 5341–5342 and references cited therein.

0022-3263/95/1960-6670$09.00/0

to its dicobalt hexacarbonyl complex II,[8] which in the presence of excess norbornadiene gave stereoselectively and in excellent yield the corresponding tricyclic enone III and its diastereomer as a separable mixture (2.5:1, 93% (58% isolated yield of **4a**) and 24:1, 82%, respectively).[3a,b] While 10-(methylthio)isoborneol in this sequence generates a much more impressive diastereomeric excess, 2-phenylcyclohexanol offers the advantage of greater availability.

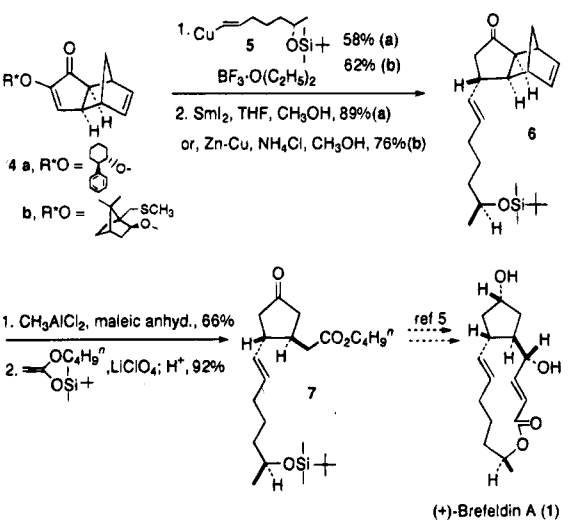
Iodide **3b**, precursor of the requisite vinylic organometallic reagent, was synthesized in stereochemically pure form from (+)-6-heptyn-2-ol (**2a**), as indicated in eq 1.[9,10] The enantiopure alcohol could be secured by bakers'



yeast (*Saccharomyces cerevisiae*) reduction of 6-heptyn-2-one.[5] The iodide was preferred over the corresponding stannane[5] because it alone could be prepared in stereochemically homogeneous form and, in addition, was found to undergo lithiation in the presence of butyllithium in diethyl ether, the solvent of choice for Yamamoto conjugate addition,[11] much more rapidly and cleanly than the stannane.

The organocopper reagent **5** (Scheme 2) was generated from this vinyllithium derivative with CuI and then treated with $BF_3{\cdot}O(C_2H_5)_2$ and the α-alkoxy enone **4a** or **4b** at −78 °C to give reproducibly in ca. 60% yield after chromatography the pure conjugate addition product. *No adduct resulting from β* (cis) attack was found. Reductive

Scheme 2



removal (with recovery) of the auxiliary was best accomplished with SmI_2[12] for the adduct from **4a** and with Zn in the presence of NH_4Cl[13] for that from **4b** to produce cleanly the expected tricylic ketone **6** (89% and 76%, respectively).

The Lewis-acid mediated retro Diels–Alder reaction under Grieco's conditions[14] readily furnished a new cyclopentenone, which under lithium perchlorate catalysis experienced uniquely trans ketene acetal addition[15] to yield on acidic workup the known (+)-brefeldin A precursor **7**. This substance, whose identity was confirmed by direct spectroscopic and chromatographic comparison with a sample of the authentic intermediate,[5] was shown to be enantiopure (≥98%) by ^{13}C NMR analysis of the acetal derivative formed with (−)-2,3-butanediol.[16]

In summary, the first application of a novel, intermolecular asymmetric Pauson–Khand reaction has led to a formal total synthesis of natural brefeldin A. Additional synthetic applications and the study of other methods for chirality control are planned.

Acknowledgment. We thank Prof. J. Lhomme for his interest in our work, Dr. N. Kardos for some preliminary experiments, and the CNRS (URA 332) and CIRIT-CICYT (Grant QFN 93-4407) for financial support. Fellowship awards from Capes (Brazil) to V.B. and the Wenner-Gren Center Foundation and the Swedish National Sciences Research Council to N.K. are gratefully acknowledged.

Supporting Information Available: Complete experimental procedures with spectral and analytical data for the synthesis of the iodide **3b** and the conversion of cycloadducts **4a** and **4b** into **7** (7 pages).

JO951462B

(8) Bernardes, V.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Greene, A. E. *J. Organomet. Chem.* **1994**, *470*, C12–14.

(9) Zweifel, G.; Lewis, W. *J. Org. Chem.* **1978**, *43*, 2739–2744.

(10) Yields are for purified, chromatographically homogeneous substances. Physical data for key compounds follows. Iodide **3b**: $[\alpha]^{20}_D$ +8° (*c* 0.9, chloroform); IR 3060, 2940, 2860, 1600, 1460, 1370, 1250, 1130, 1100, 1030, 1000, 940, 840, 810, 770 cm^{-1}; ^1H NMR (200 MHz) δ 6.55 (m, 1 H), 5.97 (dt, *J* = 1.4, 14.4 Hz, 1 H), 3.83 (m, 1H), 2.08 (m, 2 H), 1.49–1.28 (m, 4 H), 1.10 (d, *J* = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 146.5 (CH), 74.4 (CH), 68.2 (CH), 38.8 (CH_2), 36.0 (CH_2), 25.8 (CH_3), 24.4 (CH_2), 23.8 (CH_3), −4.4 (CH_3), −4.8 (CH_3); mass spectrum (EI) *m/z* 355 (M^+ + 1), 297 (M^+ − 57, 100), 255, 223, 185, 133. HRMS *m/e* calcd for $C_{13}H_{27}OISi$ (M^+) − $C(CH_3)_3$ 297.0172, found 297.0170. Ketone **6**: $[\alpha]^{20}_D$ +62° (*c* 1.8, chloroform); IR 3050, 2930, 2850, 1730, 1460, 1370, 1250, 1140, 1100, 1030, 840, 810, 770, 690 cm^{-1}; ^1H NMR (200 MHz) δ 6.14 (m, 2 H), 5.43 (m, 2 H), 3.76 (m, 1 H), 3.09 (s, 1 H), 2.78 (s, 1 H), 2.50-1.20 (m, 13 H), 1.09 (d, *J* = 6.1 Hz, 3 H), 0.87 (s, 9 H), 0.27 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 217.5 (C), 138.3 (CH), 137.5 (CH), 133.6 (CH), 130.0 (CH), 68.4 (CH), 54.5 (CH), 49.7 (CH_2), 49.7 (CH), 46.7 (CH), 44.9 (CH), 44.5 (CH_2), 42.7 (CH), 39.0 (CH_2), 32.3 (CH_2), 25.9 (CH_3), 25.4 (CH_2), 23.7 (CH_3), 18.1 (C), −4.4 (CH_3), −4.8 (CH_3); mass spectrum (EI) *m/z* 251 (M^+ − (66 + 57), 100), 195, 177, 155, 91, 75, 66; HRMS *m/e* calcd for $C_{23}H_{38}O_2Si$ (M^+) + H 375.2719, found 375.2745. Enone (retro Diels–Alder): $[\alpha]^{25}_D$ +113° (*c* 1.0, chloroform); IR 3030, 2930, 2860, 1720, 1590, 1460, 1380, 1250, 1180, 1140, 1030, 840, 770 cm^{-1}; ^1H NMR (200 MHz) δ 7.50 (dd, *J* = 2.5, 5.6 Hz, 1 H), 6.14 (dd, *J* = 2.1, 5.6 Hz, 1 H), 5.49 (m, 2 H), 3.75 (m, 1 H), 3.52 (m, 1 H), 2.60 (dd, *J* = 6.6, 18.9 Hz, 1 H), 2.09 (dd, *J* = 2.4, 18.9 Hz, 1 H), 2.00 (m, 1 H), 1.38–1.23 (m, 5 H), 1.09 (d, *J* = 6.0 Hz, 3 H), 0.90 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (50.3 MHz) δ 167.3 (CH), 133.6 (CH), 132.5 (CH), 129.7 (CH), 68.4 (CH), 44.1 (CH_2), 41.5 (CH), 39.1 (CH_2), 32.4 (CH_2), 25.9 (CH_3), 25.4 (CH_2), 23.8 (CH_3), 18.1 (C),-4.4 (CH_3), −4.8 (CH_3); mass spectrum (CI) *m/z* 326 (M^+ + 18), 309 (M^+ + 1, 100), 251, 177; HRMS *m/e* calcd for $C_{18}H_{32}O_2Si$ (M^+) + Li 315.2332, found 315.2344.

(11) Yamamoto, Y. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 947–959.

(12) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135–1138.

(13) Johnston, B. D.; Slessor, K. N.; Oehlschlager, A. C. *J. Org. Chem.* **1985**, *50*, 114–117.

(14) Grieco, P. A.; Abood, N. *J. Org. Chem.* **1989**, *54*, 6008–6010.

(15) Reetz, M.; Fox, D. N. A. *Tetrahedron Lett.* **1993**, *34*, 1119–1122. The ketene acetal was prepared in analogy with a published procedure: Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, *3*, 67–72.

(16) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183–2186.