A New Total Synthesis of (+)-Brefeldin C

Sylvie Archambaud, Karine Aphecetche-Julienne, André Guingant*

Laboratoire de Synthèse Organique, UMR CNRS 6513, FR CNRS 2465, Faculté des Sciences et des Techniques,
2 rue de la Houssinière, BP 92208 - 44322 Nantes Cedex 03, France
Fax +33(2)51125402; E-mail: guingant@chimie.univ-nantes.fr

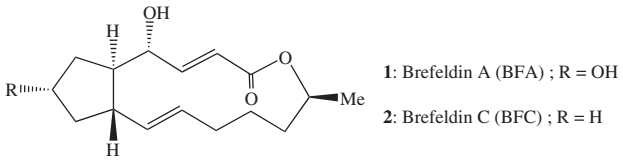
Received 2 September 2004

Abstract: A new synthesis of (+)-brefeldin C featuring a Bolm desymmetrisation reaction, a B-alkyl Suzuki–Miyaura cross-coupling and a Carreira alkynylation reaction as the key steps is reported.

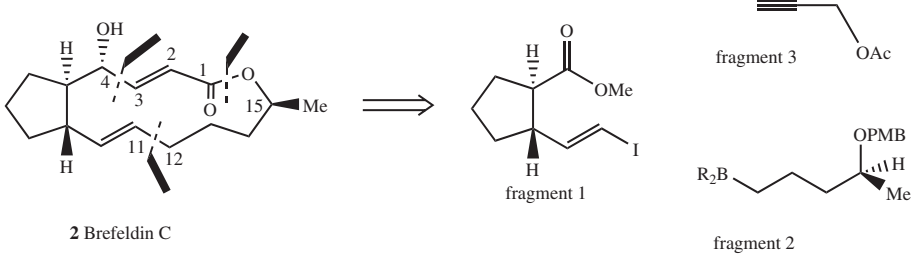
Key words: brefeldin C, Bolm desymmetrisation reaction, B-alkyl Suzuki–Miyaura cross-coupling, Carreira alkynylation reaction, total synthesis

Brefeldin A (BFA) **1** (Scheme 1) is a naturally occurring 16-membered macrolide antibiotic first isolated[1] from *Penicillium decumbens* and subsequently identified as a metabolite from several other ascomycetes sources.[2] BFA exhibits a diversity of biological activities, which include antiviral and antitumor effects.[3] BFA is also an important tool for cell biologists due to its dramatic effects on the structure and functioning of intracellular organelles, particularly the Golgi apparatus.[4] Therefore, BFA, and its direct biosynthetic precursor brefeldin C (BFC), offer promising opportunities for the development of structural analogs useful for biological evaluation and study of intracellular vesicular trafficking.

Herein, we report a new synthesis of natural (+)-BFC featuring the construction and union of three principal fragments resulting from the sequential disconnection of the C1-O σ-bond as well as the C3-C4 and C11-C12 σ-bonds of the macrocyclic lactone as outlined in Scheme 2.



Scheme 1 Structures of naturally occurring brefeldins A and C.

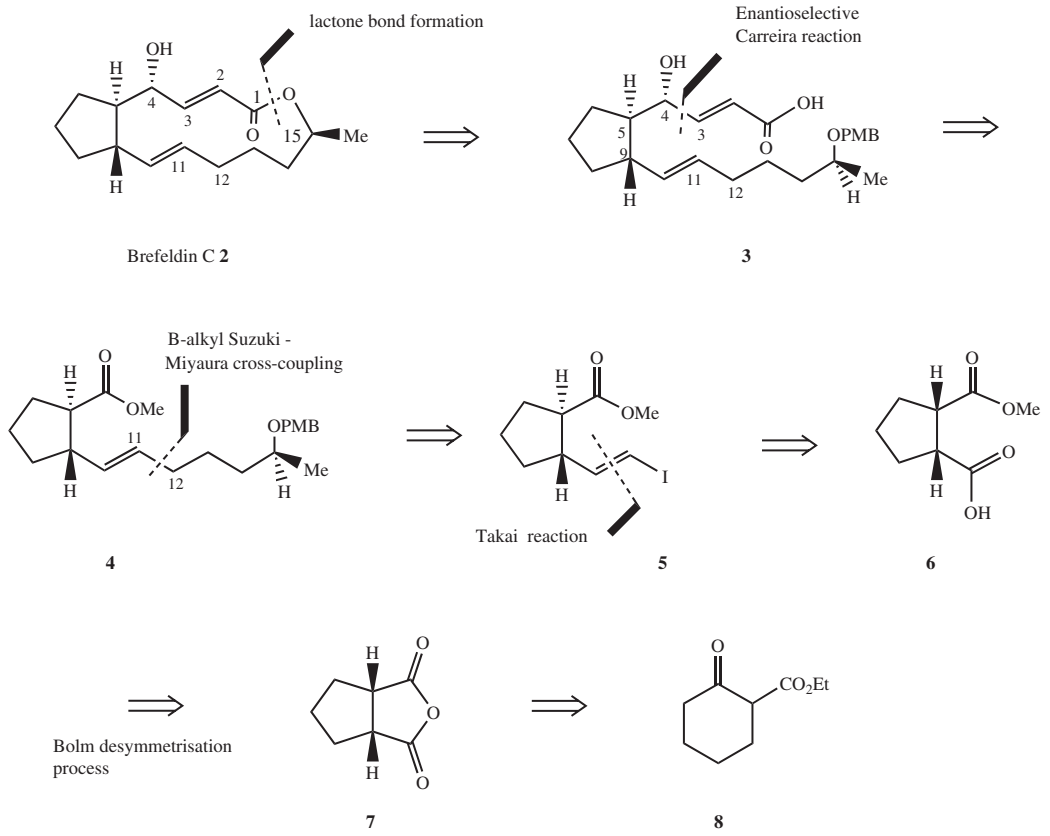


Scheme 2 The key disconnections.

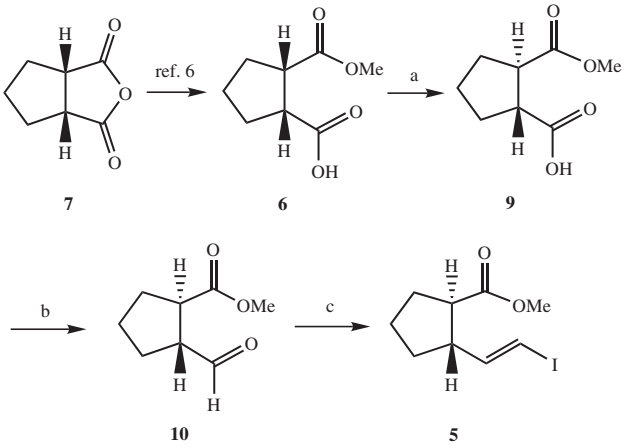
As depicted in Scheme 2 and Scheme 3, union of fragments 1 and 2 was envisaged via a palladium-mediated B-alkyl Suzuki–Miyaura cross-coupling reaction.[5] We planned to synthesise fragment 1 (**5**) from acid-ester **6**, the synthesis of which was already reported[6] through a desymmetrisation process of *meso* anhydride **7**, whereas the synthesis of fragment 2 was envisaged via opening of commercially available (*S*)-2-methyl-oxirane with an organometallic species. After functional group transformation (ester to aldehyde), application of the recently developed Carreira protocol[7] for the enantioselective synthesis of propargylic alcohols was envisioned for the attachment of fragment 3 with concomitant control of the absolute configuration at C4.

Our synthesis of fragment 1 (Scheme 4) thus commenced with the desymmetrisation reaction of anhydride **7** available in multi-gram quantities from β-keto ester **8** through a three-step sequence of known reactions (59% overall yield).[8] Applying the Bolm protocol[6] to **7** afforded acid-ester **6** in 99% yield and with 94% ee, in complete agreement with the reported data. To establish the future C5 chiral centre of BFC with proper stereochemistry, acid-ester **6** was cleanly epimerised to **9** upon treatment with potassium *tert*-butoxide in THF (92% yield). Chemoselective acid to aldehyde transformation was best accomplished in a two-step sequence (BH_3 overreduction to an alcohol, followed by oxidation under Swern conditions) to provide aldehyde-ester **10** in 58% overall yield. To complete the synthesis of **5** (fragment 1), aldehyde **10** was subjected to the conditions of the Takai reaction (excess chromium chloride in a 1:6 THF–dioxane mixture for 72 h)[9] to afford the vinylic iodide **5** in 75% isolated yield and in excellent selectivity (*E*:*Z* isomer ratio = 97:3).

SYNLETT 2005, No. 1, pp 0139–0143
Advanced online publication: 12.11.2004
DOI: 10.1055/s-2004-835669; Art ID: D26604ST



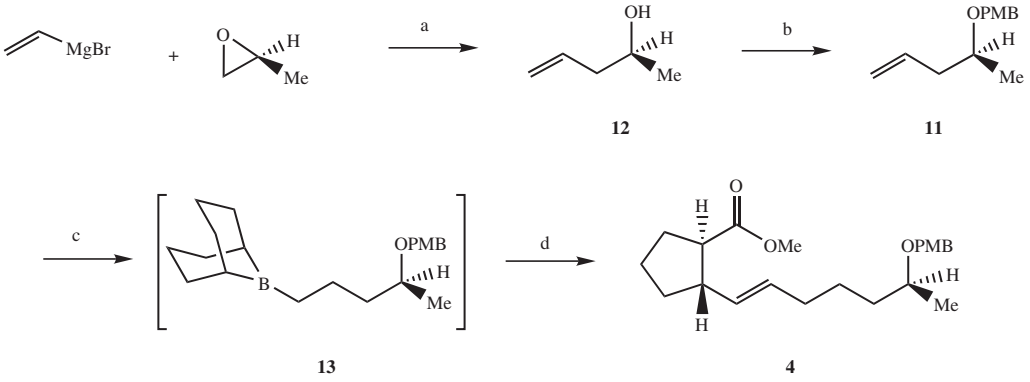
Scheme 3 Strategic pathway to brefeldin C.



Scheme 4 *Reagents and conditions*: a) *tert*-BuOK (1.5 equiv), THF, 0 °C to r.t., 1 h then HCl (6 N), 92%; b) $BH_3{\cdot}SMe_2$ (3 equiv), THF, –20 °C to r.t., 12 h, 60%; c) $(COCl)_2$ (1.1 equiv), DMSO (2.2 equiv), CH_2Cl_2, –60 °C, 15 min then DIEA (5 equiv), –60 °C to r.t., 96%; d) $CrCl_2$ (5 equiv), CHI_3 (2 equiv), THF–dioxane (1:6), 25 °C, 72 h, 75%.

The synthesis of alkene **11** (precursor of fragment 2, Scheme 5) was achieved in two simple steps featuring epoxide-opening of (*S*)-2-methyl-oxirane with vinylmagnesium bromide in the presence of CuCl(COD)[10] to give **12**, followed by protection of the secondary hydroxyl group as a *p*-methoxybenzyl ether (PMB). With the requisite fragment 1 and alkene **11** in hand, we were now in a position to attempt their union to give **4**. Towards this end, alkene **11** was first subjected to hydroboration conditions (9-BBN-H, followed by addition of a base) to form the B-alkyl-9-BBN intermediate **13** (fragment 2). To this intermediate was then added vinylic iodide **5** in conjunction with a Pd(0) catalyst system.[5] After numerous investigations of the influence of both the catalyst and the base it was found that $[Pd(dppf)Cl_2{\cdot}CH_2Cl_2]$ (0.1 equivalent) and Cs_2CO_3 (2 equivalents) were the reagents of choice. Under these conditions the cross-coupling proceeded in 6 hours at 30–35 °C in THF–DMF to give **4** in excellent isolated yield (90%) along with minimum formation of homo-coupling product (ca. 4% observed in the crude material).

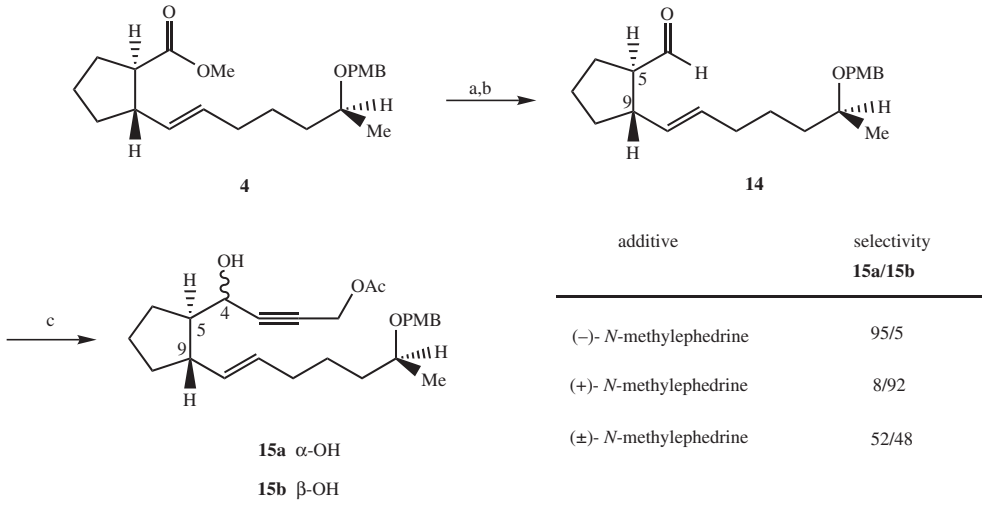
Having successfully addressed the connection of fragments 1 and 2, the next task at hand was to operate a functional group interconversion (ester **4** to aldehyde **14**) and to install the remaining side chain (fragment 3) with control of the absolute configuration of the stereogenic centre at C4 (BFC numbering). In the event, the requisite aldehyde **14** was readily prepared from ester **4** following a reduction–oxidation sequence (75% for two steps, Scheme 6). At this stage, examination of molecular models suggested that the C5 and C9 stereogenic centres would be of little utility to control the challenging C4 stereocentre. A strategy based on reagent control was thus judged more adapted to install the C4 hydroxyl group with the requisite absolute configuration. Following this idea,



Scheme 5 *Reagents and conditions*: a) (2*S*)-2-methyl-oxirane, THF, –78 °C, then CuCl(COD) (0.1 equiv), vinylmagnesium bromide (1.5 equiv), –78 °C to r.t., 15 h; b) NaH (3 equiv), DMF, **12**, PMBCl (2 equiv) in THF (DMF–THF 5:1), 0 °C to r.t., 15 h, 94% (2 steps); c) **11** (1 equiv), THF, 9-BBN (2 equiv), 30 °C, 3 h; d) 3 M aq Cs_2CO_3 (1.5 equiv), **5** (0.76 equiv) in DMF (DMF–THF 1:1), [Pd(dppf)Cl_2·CH_2Cl_2] (0.076 equiv), 30 °C, 6 h, 90%.

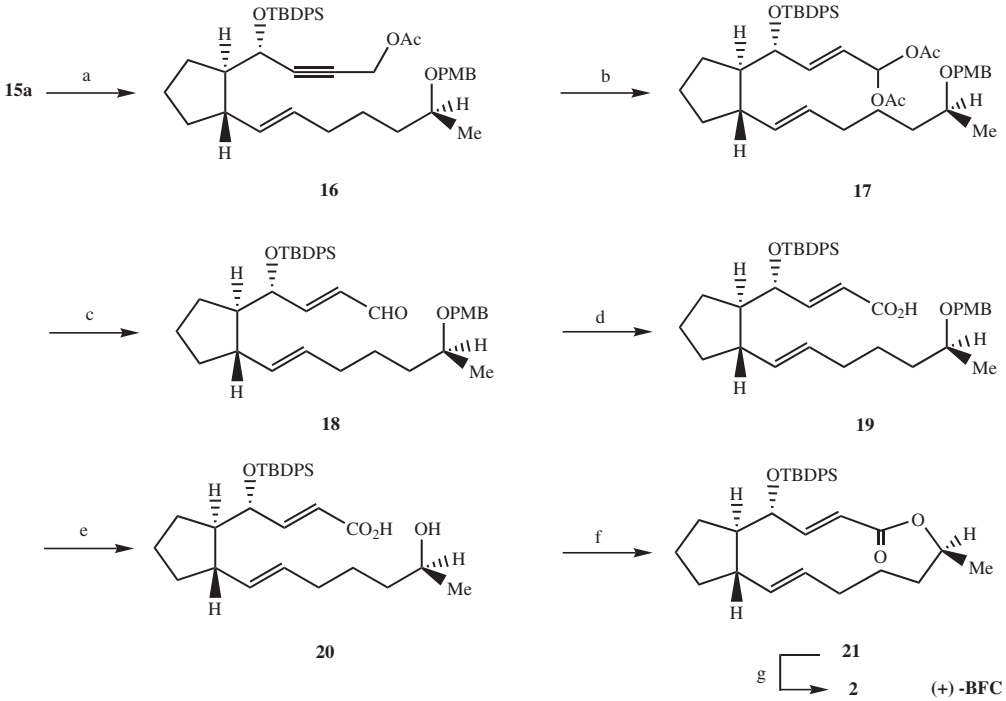
our attention was attracted by the Carreira's protocol, which makes use of in situ generated zinc alkynylides associated with a chiral amine as nucleophilic species to generate chiral propargylic alcohols from aldehydes with a high degree of enantioselectivity. A further motivation for this strategy came from the fact that a propargylic acetate structure may be transformed into an (*E*)-α,β-unsaturated aldehyde,[11] the oxidation of which would furnish an (*E*)-α,β-unsaturated acid unit ultimately required for the macrolactonisation step (Scheme 3). To test the viability of the projected alkynylation route, aldehyde **14** was exposed to propargylic acetate in the presence of zinc triflate, triethylamine and (–)-*N*-methylephedrine under the reported conditions. The required propargylic alcohol **15a** was then isolated in excellent chemical yield and with a good diastereoselectivity (95:5).[12] As shown in Scheme 6, switching (–)-*N*-methylephedrine to its (+)-enantiomer afforded epimeric alcohol at C4 with a somewhat lower diastereoselectivity whereas, in the presence of racemic *N*-methylephedrine, the reaction proceeded reluctantly to give a mixture of propargylic alcohols in low yield and with an almost total lack of diastereoselectivity. Thus, it does appear that, as originally forecasted, the stereochemistry of the catalyst is the dominating stereocontrol element of the reaction.

With propargylic alcohol **15a** now in hand, the next objective was its transformation into (*E*)-α,β-unsaturated acid **19**. This was accomplished in four efficient steps as illustrated in Scheme 7. Thus, after silylation of the hydroxyl group at C4, the resulting TBDPS ether was treated with a palladium source in acetic acid to give allylic *gem*-diacetate **17**, which, without purification, was exposed to the action of triethylamine in methanol to give aldehyde **18**. Key acid **19** was finally accessed by oxidation of **18** with sodium chlorite in *tert*-BuOH. The synthesis of (+)-BFC was now well within reach, with only macrocyclisation and deprotection of alcohol functionalities as required steps. Towards this end, PMB cleavage was first



additive	selectivity **15a/15b**
(–)- *N*-methylephedrine	95/5
(+)- *N*-methylephedrine	8/92
(±)- *N*-methylephedrine	52/48

Scheme 6 *Reagents and conditions*: a) $LiAlH_4$, Et_2O, 0–25 °C, 3 h, 85%; b) $(COCl)_2$ (1.1 equiv), DMSO (2.2 equiv), CH_2Cl_2, –60 °C, 15 min then DIEA (5 equiv), –60 °C to r.t., 89%; c) $Zn(OTf)_2$ (4.2 equiv), (–)-*N*-methylephedrine (3.2 equiv), Et_3N (3.2 equiv), toluene, 23 °C, 2 h then propargylic acetate (3.2 equiv), 23 °C, 15 min then **14** (1 equiv), 23 °C, 24 h, 93%.



Scheme 7 *Reagents and conditions*: a) **15a** (1 equiv), DMF, imidazole (2.5 equiv), TBDPSCl (1.2 equiv), 0 °C to r.t., 12 h, 96%; b) $Pd(PPh_3)_4$ (0.05 equiv), PPh_3 (0.6 equiv), toluene, HOAc (1.5 equiv), r.t., 20 min then **16** (1 equiv), 110 °C, 1 h, 51% (+33% of **18**); c) **17**, MeOH, Et_3N (3.25 equiv), r.t., 12 h, 80%; d) **18**, 2-methyl-2-butene (120 equiv), *tert*-BuOH, 0 °C then NaO_2Cl (1.5 equiv), $NaH_2PO_4{\cdot}2H_2O$ (1.5 equiv), H_2O (*tert*-BuOH–H_2O 1.25:1), r.t., 24 h, 98%; e) **19**, CH_2Cl_2–H_2O (20:1), DDQ (1.5 equiv), r.t., 12 h, 78%; f) **20**, THF, Et_3N (1.4 equiv), 2,4,6-trichlorobenzyl chloride (1.12 equiv), r.t., 8 h then toluene (toluene–THF 10:1), addition to DMAP (6.8 equiv) in toluene, reflux, 16 h, 79%; g) **21**, THF, *n*-Bu_4NF (1.5 equiv), r.t., 6 h, 78%.

accomplished with DDQ in CH_2Cl_2 at ambient temperature to give the hydroxy acid **20**, which was next cyclised via its Yamaguchi mixed anhydride[13] to afford the desired macrocyclic lactone **21** isolated in 79% yield after chromatography. Finally, deprotection of the silyl ether with TBAF in THF completed the assembly of (+)-brefeldin C (Scheme 7). The spectroscopic (^1H NMR, ^{13}C NMR, HRMS) and physical properties (melting point, optical rotation) were identical in all respects with those of natural BFC. Moreover, an X-ray crystallographic study[14] unambiguously confirmed the structure and stereochemistry of the synthetic BFC, revealing its virtually identical solid-state conformation with that of BFA.

In conclusion, a convergent and highly stereocontrolled total synthesis of (+)-brefeldin C was accomplished beginning with the desymmetrisation of anhydride **7**. The palladium-mediated Suzuki cross-coupling and the Carreira alkynylation reaction were the keystones of the strategy for the stereoselective union of fragments 2 and 3 to the chiral acid-ester **6**. Overall, this synthesis required a total of 16 steps in its longest linear sequence with an overall yield of ca. 4.6%. We are currently developing an analogous, modular strategy for the synthesis of a small library of BFA and BFC analogues.

Acknowledgment

This work was supported by grants from the CNRS and INSERM ('Physique et Chimie du Vivant' and 'Molécules et Cibles Thérapeutiques'). We are indebted to D. Brégeon for preliminary experiments, to M.-J. Bertrand for technical assistance and to Pr. J. Lebreton (Université de Nantes) and Dr J. Cherfils (LEBS, CNRS, Gif sur Yvette) for useful discussions.

References

(1) Singleton, V. L.; Bohonos, N.; Ullstrup, A. J. *Nature* **1958**, *181*, 1072.
(2) (a) Betina, V.; Nemec, P.; Dobias, J.; Barath, Z. *Folia Microbiol.* **1962**, *7*, 353. (b) Härri, E.; Loeffler, W.; Sigg, H. P.; Stähelin, H.; Tamm, C. *Helv. Chim. Acta* **1963**, *46*, 1235. (c) Stolk, A. C.; De Scott, B. *Persoonia* **1967**, *4*, 391. (d) Suzuki, Y.; Tanaka, H.; Aoki, H.; Tamura, T. *Agric. Biol. Chem.* **1970**, *34*, 395. (e) Sovova, M.; Opletal, L.; Hanus, V.; Knezova, E. *Pharmazie* **1992**, *47*, 395. (f) Abraham, W.-R.; Arfmann, H.-A. *Planta Medica* **1992**, *58*, 484.
(3) Betina, V. *Folia Microbiol.* **1992**, *37*, 3.
(4) Sciaky, N.; Presley, J.; Smith, C.; Zaal, K. J. M.; Cole, N.; Moreira, J. E.; Terasaki, M.; Siggia, E.; Lippincott-Schwartz, J. *J. Cell Biol.* **1997**, *139*, 1137; and references cited therein.
(5) For recent reviews, see: (a) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 4544.
(6) (a) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195. (b) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984.

(7) (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) El Sayed, E.; Anand, N. K.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 3017.
(8) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817.
(9) (a) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408. (b) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.
(10) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990.
(11) (a) Trost, B. M.; Brieden, W.; Baringhaus, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1335. (b) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **2001**, *123*, 3671.
(12) Alcool **15a** was separated from its minor diastereoisomer **15b** by column chromatography on silica (eluent: petroleum ether–EtOAc, 4:1). At this stage, the absolute configuration at C4 was tentatively assigned on the basis of precedent[7] and was confirmed later by the obtention of (+)-BFC.
(13) Inaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Soc. Chem. Jpn.* **1979**, *52*, 1989.
(14) We thank Pr. M. Evain (Institut des Matériaux Jean Rouxel, Nantes) for X-ray analysis.