Enantioselective Synthesis of an Advanced Intermediate for the Synthesis of Brefeldin A and Analogues

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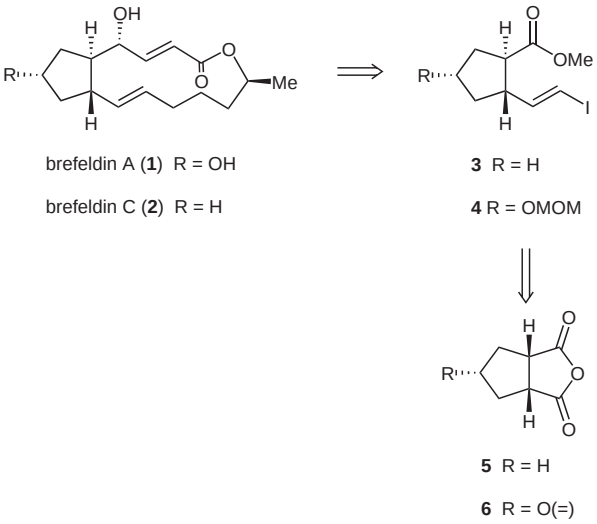
Abstract: A synthesis of methyl (1*R*,2*R*,4*S*)-2-[(*E*)-2-iodovinyl]-4-(methoxymethoxy)cyclopentanecarboxylate is described in nine steps from a prochiral anhydride. A desymmetrization reaction followed by an epimerization and a Takai reaction are the key steps of the transformation. Based on previous work, this vinylic iodide product should be a useful precursor for the synthesis of brefeldin A and analogues.

Key words: brefeldin A, desymmetrization reaction, Takai reaction

Guanine-nucleotide exchange factors (GEF) are proteins that activate small GTP-binding proteins (G-proteins) by allowing the dissociation of the tightly bound GDP nucleotide and its replacement by a GTP. In their activated form the small G proteins interact with protein effectors to which they transmit signals of action. Signal transduction, cellular traffic, and organization of the cytoskeleton are all regulated by small G-proteins so that these proteins, and their associated GEF, appear as potential targets for therapeutic intervention.[1] However, because a GEF is not specific for a given G-protein, competitive inhibitors of G-protein–GEF interactions may well block several transduction pathways causing deleterious cellular effects. Brefeldin A (**1**), a macrolide lactone first isolated[2] from *Penicillium decumbens*, presents the rare and distinct advantage of being an in vivo noncompetitive inhibitor of the activation of the small G-protein Arf1, an essential regulator of membrane traffic at the Golgi, by its GEF. In fact, **1** was shown to bind in a cavity at the interface between Arf-GDP and the catalytic domain of the GEF (called the Sec7 domain) thus stabilizing a transient reaction intermediate (interfacial inhibition).[3] Recently, we reported[4] an enantioselective synthesis of brefeldin C (**2**), a biological precursor of **1** lacking the hydroxyl group at C7, from a chiral substituted cyclopentane precursor **3**, itself prepared from the prochiral anhydride **5** (Scheme 1). Subsequently, comparative studies of the inhibition of the nucleotide exchange reaction using both **1** and **2** showed that the hydroxyl group at C7 in **1** plays a crucial role in this process due to the establishment of a hydrogen bond with a tyrosine residue (Tyr 190) of the Sec7 domain.[5] In order to best delineate the mode of action of **1**, it is thus of importance to synthesize several analogues of this molecule displaying structural modifications on the thirteen-membered lactone ring while retaining the OH at C7. We thus thought that a cyclopentane derivative such as **4**, substituted at its C4 position by a MOM-protected hydroxyl group, would be an efficient scaffold to prepare analogues of **1**. In this paper, we detail the extension of our initial protocol to the successful enantioselective synthesis of **4** from the prochiral anhydride **6**.



Scheme 1

The synthesis of **6** commences with the 3a,4,7,7a-tetrahydro-2-benzofuran-1,3-dione (**7**, tetrahydrophthalic anhydride) which was transformed into keto diester **8** following a reported three-step procedure[6] with slight modifications. Although formation of keto diacid **9** could be effected by saponification of **8**, it was found most appropriate, both in terms of efficiency and practicability, to prepare **9** by acidic hydrolysis[7] of **8**. Cyclization of **9** to form anhydride **6** was best accomplished in acetyl chloride at reflux.[8] In contrast to its nor-carbonyl analogue,[4] keto diacid **9** failed to give **6** in practical yields when treated with acetic anhydride or under several other conditions.[9] Thus, following the reaction sequence shown in

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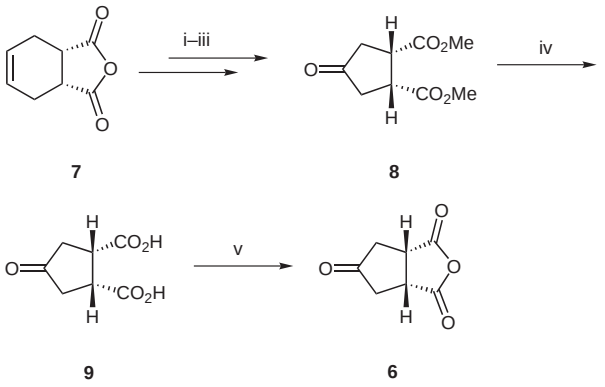
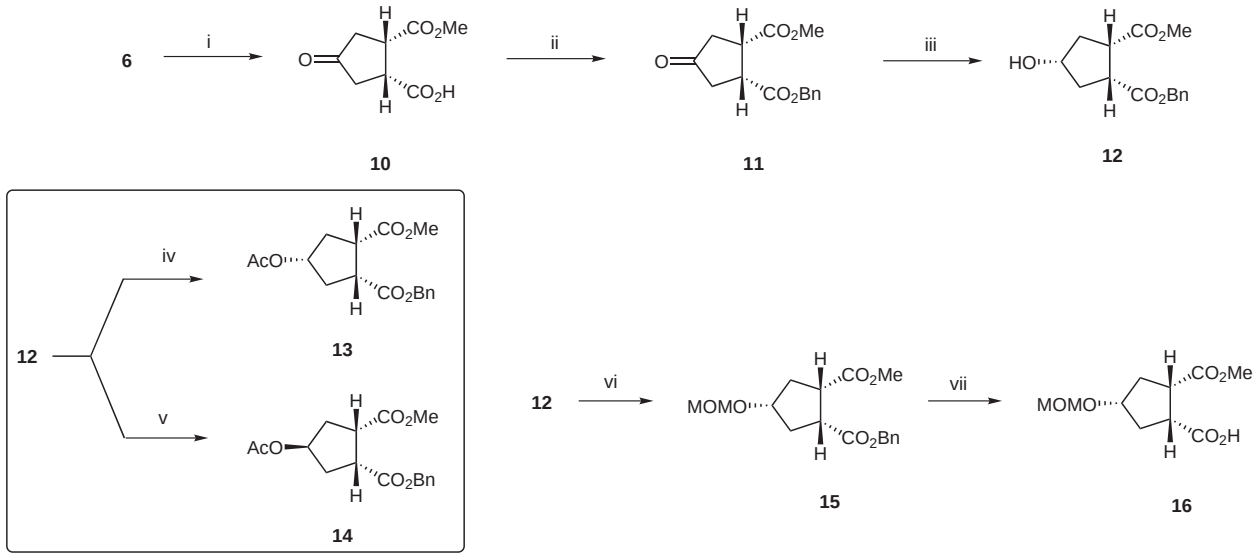


Scheme 2 *Reagents and conditions*: (i) concd H_2SO_4 (10 equiv), MeOH, reflux, 18 h, 96%; (ii) preceding crude product, aq $KMnO_4$, 20 °C, 5 h, then Na_2SO_4, then pH lowered to 1–2 with 12 N aq HCl, 96%; (iii) preceding crude product, NaOAc, Ac_2O, reflux, 6 h, then purification by chromatography (EtOAc–PE, 1:1) followed by crystallization (hot Et_2O), 82%; (iv) 10% aq HCl, reflux, 6 h, 99%; (v) AcCl, reflux, 3 h then filtration (→ **6**, 55%); filtrate concentrated in vacuo, residue heated at 100 °C for 2 h under a pressure of 1–2 mm Hg, then cooled to 20 °C and taken up in CH_2Cl_2, filtration (→ **6**, 30%; 85% total yield).

Scheme 2 (steps 1–5), anhydride **6** could be routinely prepared on a multigram scale in 66% overall yield.

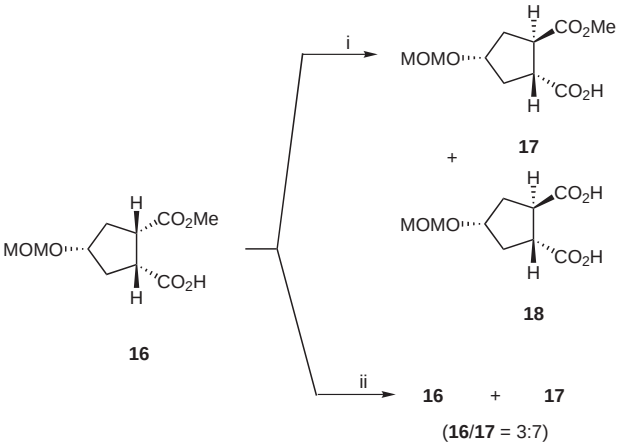
With the prochiral anhydride **6** in hand we were now in a position to study its desymmetrization reaction to give the (1*R*,2*S*)-2-(methoxycarbonyl)-4-oxocyclopentanecarboxylic acid (**10**). In our earlier investigations, we used the efficient Bolm's conditions[10] to desymmetrize anhydride **5**. However, when applying these conditions to **6** {i.e. quinidine, toluene, –55 °C, 4 d, [**6**] = 0.1 M}, the enantiomeric excess of **10** was only of 60%. Looking for other conditions we found that the patent literature[11] reported the desymmetrization of **6** to give **10** in 84% ee by treatment with methanol and a catalytic amount of hydroquinidine (anthraquinone-1,4-diyl)diether [$(DHQD)_2AQN$]. Trying to reproduce the conditions prescribed we discovered that the anhydride concentration (not mentioned in the patent) was a crucial parameter to achieve an optimal enantiomeric excess. In the best conditions found {MeOH (10 equiv), $(DHQD)_2AQN$ (0.10 equiv), MeO*t*-Bu, –30 °C for 90 h; [**6**] = 0.02 M} an enantiomeric excess within the range of 80–88% could be attained for **10**. A direct measurement of the enantiomeric excess of **10** could not be achieved but this was easily made after transformation of **10** into its benzyl ester **11**.[12] In addition to providing an excellent UV detectability and accuracy in the determination of enantiomeric excess, the benzyl protection also facilitated, in a practical point of view, the realization of the subsequent steps (Scheme 3). Reduction of keto diester **11** could next be accomplished by exposure to L-Selectride in THF at –78 °C to give alcohol (1*R*,2*S*,4*R*)-**12** in 87% yield[13] and with an almost total control of the stereoselectivity at C4. The *R*-configuration at the newly generated chiral center of alcohol **12** could be established after the latter was transformed into the diastereomeric acetates **13** and **14** and correlation peaks between H1, H2, and H4 were observed in the NOESY spectrum of **13**. Installation of a MOM protecting group to afford **15** was readily accomplished by treatment of **12** with dimethoxymethane in the presence of P_2O_5. Reductive deprotection of the benzyl ester group of **15** afforded the key 2-(methoxycarbonyl)-4-(methoxymethoxy)cyclopentanecarboxylic acid intermediate **16** (Scheme 3).

Proceeding on to reach **4**, we next addressed the problem of epimerization at C2 of **16**. In our synthesis of **2**[4] this problem could be solved by treatment of the C4-unsubstituted analogue of **16** with KO*t*-Bu (1.5 equiv) in *t*-BuOH. Unfortunately, when applied to **16**, these conditions



Scheme 3 *Reagents and conditions*: (i) $(DHQD)_2AQN$ (0.01 equiv), anhyd *t*-BuOMe (→ [**6**] = 0.02 M), anhyd MeOH (0.1 equiv), –30 °C, 90 h, 94%; (ii) BnOH (5 equiv), DCC (1.2 equiv), cat. DMAP, CH_2Cl_2, 25–30 °C, 10 h, 86%; (iii) L-Selectride (1 M solution in THF; 1.1 equiv), THF, –78 °C, 2 h then usual workup, 87%; (iv) AcOH (2.4 equiv), DCC (1.5 equiv), cat. DMAP, CH_2Cl_2, 25–30 °C, 10 h, quant. yield; (v) Ph_3P (1.2 equiv), AcOH (1.2 equiv), DEAD (1.2 equiv), Et_2O, 20 °C, 4 h, 81%; (vi) $(MeO)_2CH_2$ (70 equiv), P_2O_5 (20 equiv), $CHCl_3$, 20 °C, 2 h, 89%; (vii) H_2, 10% Pd/C, MeOH, 20 °C, 2 h, quant. yield.

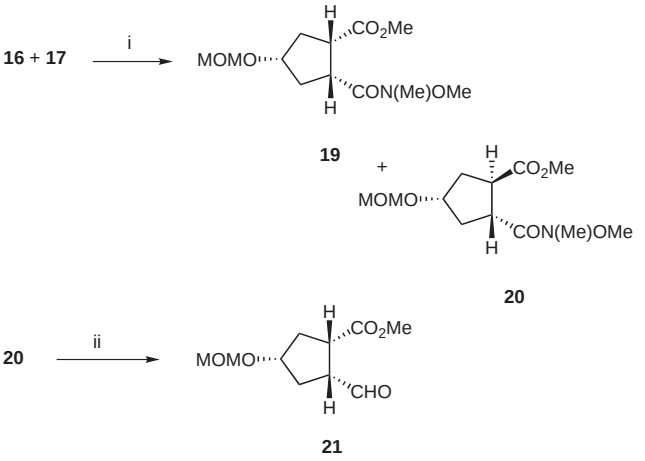
proved inefficient, affording, next to the desired (1*R*,2*R*,4*S*)-**17**, variable amounts of diacid (1*R*,2*R*)-**18**. Recognizing that diacid **18** originated during the workup of the reaction,[14] we quenched the crude reaction mixture with AcOH (6 equiv in THF) instead of the usually added aqueous 1 N HCl. Although these new conditions allowed us to isolate acid-ester **17** free of diacid **18**, the yield was unsatisfactory. Consequently, we came to favor a different route to reach **17** in reproducible conditions and satisfactory yield. Compound **16** was thus bisdeprotonated by treatment with LDA in THF at –78 °C then kinetically reprotonated (2 N HCl in Et_2O) to afford a 3:7 mixture of diastereomers **16** and **17** in quantitative yield (Scheme 4).



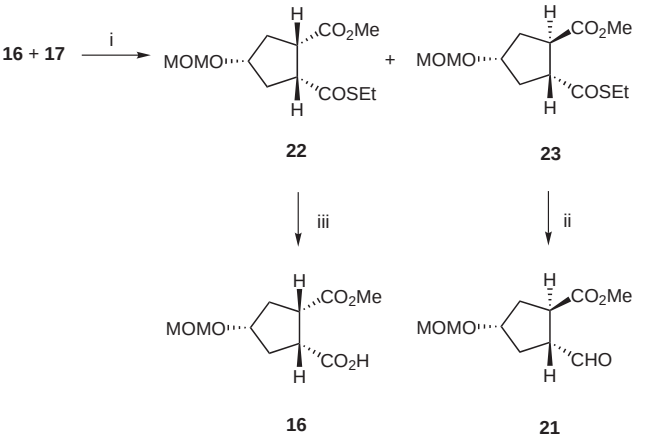
Scheme 4 *Reagents and conditions*: (i) KO*t*-Bu (1.5 equiv), 20 °C, 1 h, then 1 N aq HCl (1.5 equiv) or AcOH (3 equiv) in THF; (ii) LDA (3 equiv), –78 °C, THF, 3 h, then 2 M HCl in Et_2O, quant. yield.

This mixture of diastereomers could not be separated at this stage and was thus engaged in the subsequent step with the final aim of obtaining aldehyde **21**. A reduction–oxidation procedure, which gave us satisfactory results in earlier investigations,[4] was first attempted. However, in that case, borane reduction of a mixture of diastereomers **16** and **17** led to the corresponding diastereomeric alcohols in low yield (30%). Searching for a more practical method for the preparation of aldehyde **21**, we transformed the above mixture into the corresponding mixture of Weinreb amides **19** and **20** (Scheme 5), which, fortunately, proved easily separable by column chromatography on silica gel. Amide **20**, which was isolated in 65% yield from **16** (two steps), was next reduced to aldehyde **21** by exposure to a solution of DIBAL-H in CH_2Cl_2 (56% yield).

In a different approach to **21**, the mixture of diastereomers **16** and **17** was first transformed into a mixture of thioesters **22** and **23**, which could be separated by column chromatography on silica gel. The thioester **23**, isolated in 51% yield from **16**, was next reduced by treatment with Et_3SiH and 10% Pd/C[15] to give aldehyde **21** in 88% yield (Scheme 6). A clear advantage of this route is that acid-ester **16** can be regenerated from thioester **22** by treatment



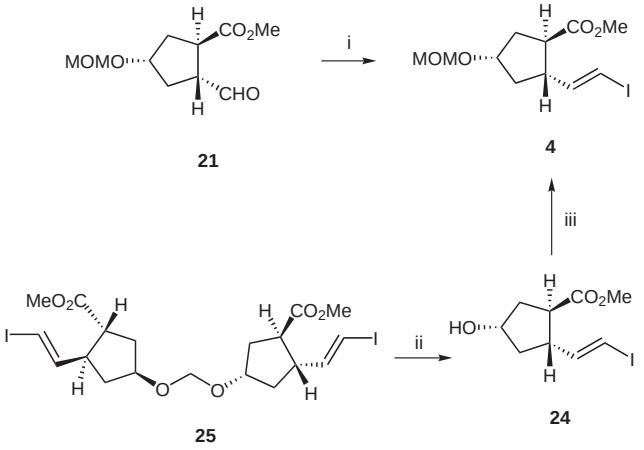
Scheme 5 *Reagents and conditions*: (i) NH(OMe)Me·HCl (1.5 equiv), NMM (1.5 equiv), EDC (1.5 equiv), CH_2Cl_2, 20 °C, 10 h, **20**: 65%, **19**: 32%; (ii) DIBAL-H in hexane (1.5 equiv), –78 °C, 3 h, 56%.



Scheme 6 *Reagents and conditions*: (i) DCC (1.2 equiv), ethanethiol (3 equiv), DMAP (0.1 equiv), CH_2Cl_2, 20 °C, 3 h, **23**: 51%, **22**: 21%; (ii) Et_3SiH (2.85 equiv), 10% Pd/C, CH_2Cl_2, 15–20 °C, 20 min, 88%; (iii) Br_2 (20 equiv), THF–H_2O (5:1), 20 °C, 1 h, quant. yield.

with Br_2[16] and can thus be recycled into the epimerization reaction.

We were now in a position to carry out the final stage of the synthesis of (1*R*,2*R*,4*S*)-**4** by application of the Takai procedure[17] to aldehyde **21**. The latter was thus exposed to the action of $CrCl_2$ (6 equiv) and iodoform (2 equiv) in a degassed mixture of 1,4-dioxane–THF[18] (6:1) at 0 °C for 72 h. After usual workup[19] and purification through a silica gel column, the target vinylic iodide **4** could be isolated along with variable quantities of alcohol **24** and its dimer **25** (Scheme 7). The structure of **25**, which was fully ascertained by X-ray crystal structure analysis (Figure 1),[20] provided an *a posteriori* confirmation of the absolute configuration attributed to aldehyde **21** and its precursors. Although **25** could be cleaved to give **24** and the latter MOM-protected to give **4**, it is clear that, in the course of a total synthesis, a more efficient way to prepare **4** must be found. After some considerable attempts, we finally discovered that modification of the original workup of the reaction, i.e. filtration of the crude mixture through



Scheme 7 *Reagents and conditions*: (i) anhyd $CrCl_2$ (5.8 equiv), CHI_3 (2 equiv), 1,4-dioxane–THF (6:1), 20 °C, 72 h, 88%, see ref. 19 for more experimental details; (ii) PhSH (5 equiv), $BF_3{\cdot}OEt_2$ (5 equiv), THF, 20 °C, 1 h, 92%; (iii) $(MeO)_2CH_2$ (70 equiv), P_2O_5 (20 equiv), $CHCl_3$, 20 °C, 1 h, 93%.

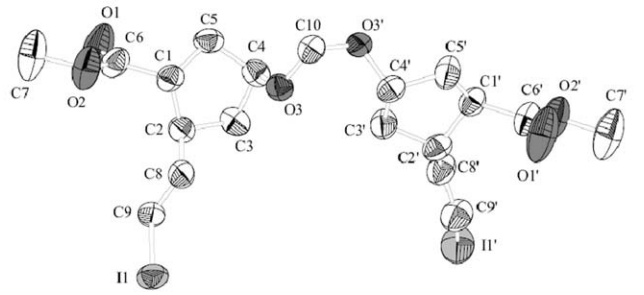


Figure 1 X-ray crystal structure of **25**

a pad of Celite and neutral alumina followed by purification through a silica gel column [elution first with hexane to remove iodoform in excess then with a EtOAc–PE mixture (1:9)] afforded **4** (*E*/*Z* = 97:3) in up to 88% and in a reproducible manner.

In conclusion, a synthesis of the methyl (1*R*,2*R*,4*S*)-2-[(*E*)-2-iodovinyl]-4-(methoxymethoxy)-cyclopentanecarboxylate (**4**) has been achieved in nine steps from the prochiral anhydride **6**. By comparison with our previous synthesis of brefeldin C, unanticipated difficulties due to the presence and (or) the sensitive nature of the OMOM group were encountered. However, we found conditions to circumvent all of these difficulties and to reach **4** in good overall yield (20% from **6**). Use of vinylic iodide **4** as a scaffold to prepare several brefeldin A analogues is under way and the results of these studies will be reported in due course.

References and Notes

(1) See, inter alia: (a) Cherfils, J.; Chardin, P. *Trends Biochem. Sci.* **1999**, *24*, 306. (b) Takai, Y.; Sasaki, T.; Matozaki, T. *Physiol. Rev.* **2001**, *81*, 153. (c) Marinissen, M. J.; Gutkind, J. S. *Trends Biochem. Sci.* **2005**, *30*, 423. (d) Zeghouf, M.; Guibert, B.; Zeeh, J.-C.; Cherfils, J. *Biochem. Soc. Trans.* **2005**, *33*, 1265. (e) Hall, A. *Biochem. Soc. Trans.* **2005**, *33*, 891.

(2) Singleton, V. L.; Bohonos, N.; Ullstrup, A. J. *Nature (London)* **1958**, *181*, 1072.

(3) See, for example: (a) Robineau, S.; Chabre, M.; Antonny, B. *Proc. Natl. Acad. Sci. U. S. A.* **2000**, *97*, 9913. (b) Renault, L.; Guibert, B.; Cherfils, J. *Nature (London)* **2003**, *426*, 525. (c) Mossessova, E.; Corpina, R. A.; Goldberg, J. *Mol. Cell.* **2003**, *12*, 1403. (d) Cherfils, J.; Pacaud, P. *Med. Sci. (Paris)* **2004**, *20*, 393. (e) Pommier, Y.; Cherfils, J. *Trends Pharmacol. Sci.* **2005**, *26*, 138.

(4) Archambaud, S.; Aphecetche-Julienne, K.; Guingant, A. *Synlett* **2005**, 139.

(5) Zeeh, J.-C.; Zeghouf, M.; Grauffel, C.; Guibert, B.; Martin, E.; Dejaegere, A.; Cherfils, J. *J. Biol. Chem.* **2006**, *281*, 11805.

(6) Gais, H. J.; Bülow, G.; Zatorski, A.; Jentsch, M.; Maidonis, P.; Hemmerle, H. *J. Org. Chem.* **1989**, *54*, 5115.

(7) Yoshihisa, M.; Yoshiyasu, T.; Kazu, A. *Chem. Pharm. Bull.* **1987**, *35*, 2266.

(8) Ballini, R.; Bosica, G.; Fiorini, D.; Righi, P. *Synthesis* **2002**, 681.

(9) Heating **9** in Ac_2O (or in Ac_2O with a catalytic amount of DMAP) at reflux failed to give anhydride **6**. Failure was also encountered while attempting distillation of **9** in the presence of a catalytic amount of sulfuric acid. However, **6** could be obtained in low yields when **9** was treated with $ClCO_2Me$ and NMM (1.1 equiv each) in THF at 20 °C for 30 min (35%) or with TFA (4 equiv) in dioxane at 75 °C for 2 h (38%).

(10) (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.

(11) (a) Deng, L.; Chen, Y.; Tian, S.-K. WO 2001074741, **2001**. (b) See also: Chen, Y.; Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2000**, *122*, 9542.

(12) Enantiomeric ratio was determined by GPC using a Lipodex E column; t_R (the injector and detector temperatures were 220 °C): 74.9 min (major enantiomer) and 76.6 min (minor enantiomer).

(13) This reaction was also performed under several other reduction conditions: $NaBH(OAc)_3$ ds (4*R*) = 90%, 76%; $NaBH_4$, ds (4*R*) = 95%, 88%; *t*-$(BuO)_3AlLiH$, ds (4*R*) = 99%, 87%.

(14) Treatment of monoacid **16** and diacid **18** with diazomethane in Et_2O afforded the corresponding *cis* and *trans* diastereomeric methyldiesters that could be easily differentiated by NMR spectroscopy [*cis*-isomer, δ = 3.67 (CO_2Me), 3.01 (H1, H2) ppm; *trans*-isomer: δ = 3.70 (CO_2Me), 3.39 (H1 or H2), 3.15 (H1 or H2) ppm].

(15) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

(16) Evans, D. A.; Willis, M. C.; Johnston, J. N. *Org. Lett.* **1999**, *1*, 865.

(17) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

(18) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497.

(19) **Preparation of Methyl (1*R*,2*R*,4*S*)-2-[(*E*)-2-Iodovinyl]-4-(methoxymethoxy)cyclopentanecarboxylate (4)**
To a suspension of anhyd $CrCl_2$ (1 g, 8.1 mmol) in anhyd and

thoroughly degassed THF (5.1 mL) were added, under a nitrogen atmosphere, recrystallized CHI_3 (1.1 g, 2.8 mmol) and aldehyde-ester **21** (300 mg, 1.4 mmol) dissolved in anhyd and thoroughly degassed dioxane (30 mL). After being stirred at r.t. for 72 h, the resulting brown reaction mixture was filtered through a pad of mixed Celite and neutral alumina. The filter cake was rinsed several times with EtOAc and the filtrate was concentrated under reduced pressure. The crude product was purified by chromatography on a column of silica gel using EtOAc and PE as eluents (0:10 then 1:9) to afford pure **4** as a colorless oil (414 mg, 1.23 mmol, 88%). The *Z*/*E* ratio at the double bond (3:97) was evaluated by ^{1}H NMR spectroscopic analysis from the area ratio of the signals of the vinylic protons.

Spectral Data and Specific Rotation

R_f = 0.5 (silica, EtOAc–PE, 1:9); $[\alpha]_D^{20}$ –42.4 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (m, 1 H, 1H3), 2.04 (m, 2 H, H5), 2.26 (m, 1 H, H3), 2.80 (m, 2 H, H1, H2), 3.35 (s, 3 H, OMe), 3.68 (s, 3 H, CO_2Me), 4.21 (m, 1 H, H4), 4.61 (s, 2 H, OCH_2O), 6.10 (d, 1 H, *J* = 14.4 Hz, CHI), 6.52 (dd, 1 H, *J* = 14.4, 7.6 Hz, vinyl CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.0 (C5), 38.8 (C3), 47.7 (C1), 48.2 (C2), 52.0 (CO_2CH_3), 55.5 (OCH_3), 75.7 (CHI), 77.0 (C4), 95.6 (OCH_2O), 148.1 (vinyl CH), 175.1 (CO_2Me). FT-IR (KBr): 3054, 2949, 1735, 1437, 1206, 1098, 1041 cm^{-1}. MS (ESI+): *m/z* 309 $[MH + MeOH]^+$; 341 $[MH]^+$; 363 $[M + Na]^+$. HRMS (ESI+): *m/z* calcd for $C_{11}H_{17}IO_4Na$: 363.0067; found: 363.0069 $[M + Na]^+$.

(20) **Crystal Data for 25**

$C_{19}H_{26}I_2O_6$, *M*r = 604.2, monoclinic, $P2_1$, *a* = 6.2760(4), *b* = 8.3184(5), *c* = 22.5860(12) Å, *β* = 96.918(8), *V* = 1170.55(12) Å^3, *Z* = 2, ρ_{calcd} = 1.714 g cm^{-3}, μ = 2.72 mm^{-1}, *F*(000) = 588, colorless needle, 0.60 × 0.11 × 0.05 mm^3, $2c_{max}$ = 60°, *T* = 298 K, 19062 reflections, 5818 unique (98% completeness), R_{int} = 0.042, 249 parameters, GOF = 1.57, *wR*2 = 0.0926, *R* = 0.0351 for 5107 reflections with $I > 2\sigma(I)$.

CCDC 660932 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.