Pergamon

Tetrahedron Letters 43 (2002) 493–497

TETRAHEDRON LETTERS

A concise enantioselective total synthesis of rhizoxin D

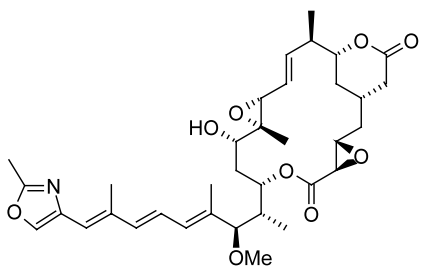
Ian S. Mitchell, Gerald Pattenden* and Jeffrey P. Stonehouse

School of Chemistry, The University of Nottingham, Nottingham NG7 2RD, UK

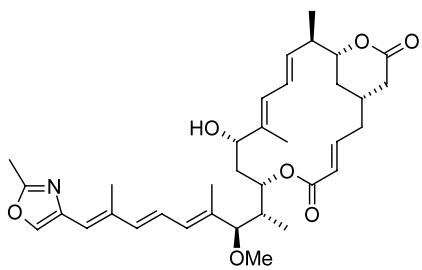
Received 15 October 2001; accepted 8 November 2001

Abstract—A new and convergent synthesis of the antitumour macrolide rhizoxin D **2** is described. The synthesis features a Wadsworth–Emmons olefination and a facile intramolecular Stille reaction to elaborate the 16-membered macrocyclic core **5** from the vinyl iodide **3** and the vinyl stannane **4** as key steps.

Rhizoxin **1** is a novel macrolide isolated from the pathogenic fungus *Rhizopus chinensis*,[1] which shows powerful antitumour and antifungal activity.[2] Indeed, the compound has now undergone extensive clinical trials as a potential drug candidate.[3] Rhizoxin D **2** is a congener of rhizoxin **1** from *R. chinensis*[4] and this didesepoxy compound is the likely biogenetic precursor of **1**. The rhizoxins have attracted considerable interest within the synthetic chemistry community,[5] and a total synthesis of rhizoxin **1**,[6] together with four total syntheses of rhizoxin D **2**,[7] have been published. We now describe a new enantioselective synthesis of rhizoxin D **2** which features a facile intramolecular Stille coupling reaction as the key step.



1



2

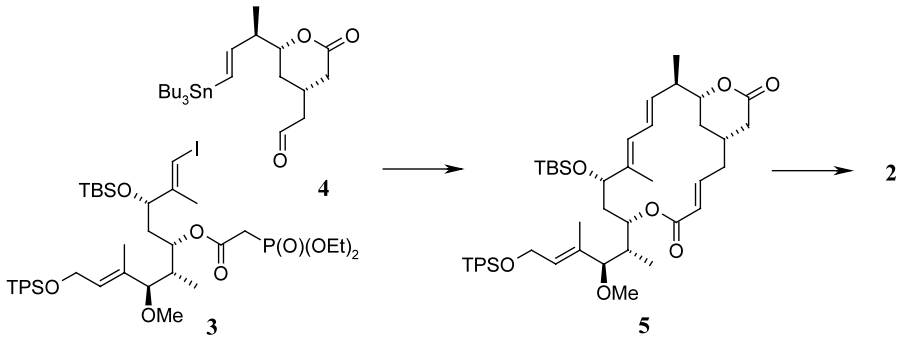
Our synthetic strategy to rhizoxin D **2** was based on elaboration of the phosphonate substituted vinyl iodide **3** and the δ-lactone substituted vinyl stannane **4** fragments, and their coupling leading to the core macrocyclic lactone **5** via a Wadsworth–Emmons olefination, followed by an intramolecular Stille reaction as key steps (Scheme 1).

Thus, an Evans aldol reaction between (*R*)-4-benzyl-3-propionyloxazolidin-2-one[8] and the known α,β-unsaturated aldehyde **6**[9] first gave the corresponding imide **7**, as a single diastereoisomer, in 85% yield. The imide **7** was next converted into the aldehyde **9** in three straightforward steps via the intermediate alcohol **8** (Scheme 2). A Mukaiyama aldol reaction between the aldehyde **9** and the silyl enol ether **10**[10] at −78°C, under chelation-control, using $AlMe_2Cl$ as the Lewis acid,[11] then gave the aldol **11** with >96% diastereoselectivity and in 81% yield. The diastereoselectivity was determined following separation of the two aldol isomers and ^1H NMR studies, in combination with comparison of NMR data with those of the alternative diastereoisomer which was produced from reaction of **9** with **10** in the presence of $BF_3{\cdot}OEt_2$.[12] Reduction of the aldol **11** using tetramethylammonium triacetoxyborohydride next led to the 1,3-*anti* diol **12**[13] which, in two steps, was converted into the key phosphonate substituted vinyl iodide **3** (Scheme 2).

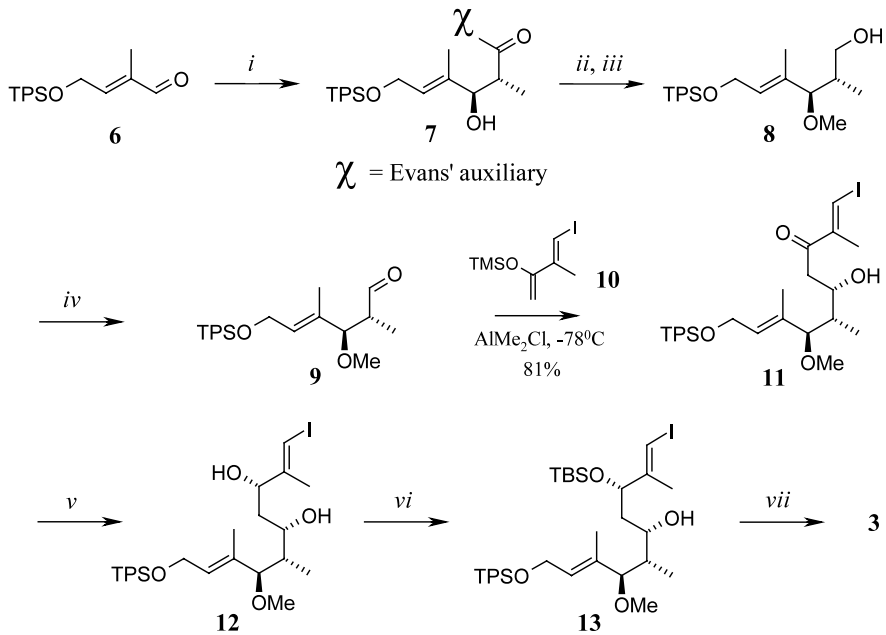
The chiral δ-lactone substituted vinyl stannane **4** was prepared starting from the known α,β-unsaturated ester **14**.[14] Reduction of **14** to the corresponding primary alcohol, followed by vinyl ether formation and Claisen

* Corresponding author.

0040-4039/02/$ - see front matter
PII: S0040-4039(01)02154-2



Scheme 1.



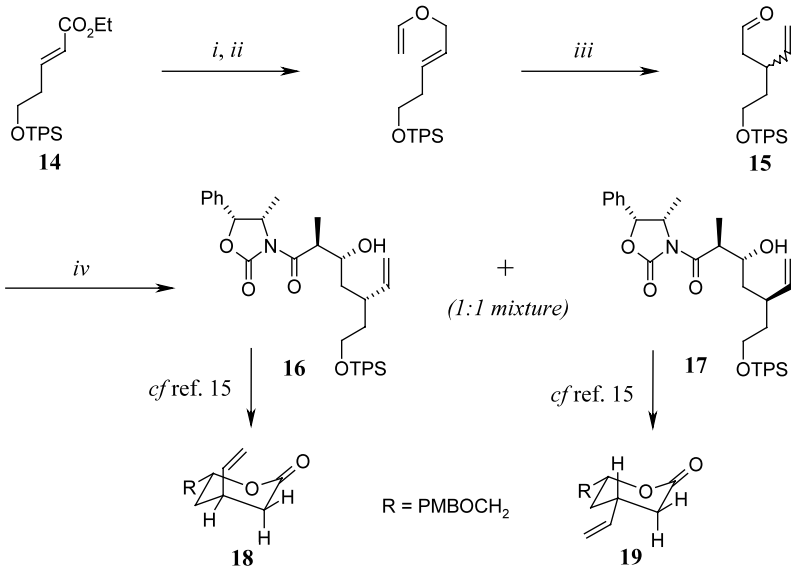
Scheme 2. *Reagents and conditions*: (i) Bu_2BOTf, Et_3N, (*R*)-4-benzyl-3-propionyloxazolidin-2-one, CH_2Cl_2, −78°C→0°C, 85%; (ii) MeOTf, 2,6-di-*tert*-butyl-4-methylpyridine, $CHCl_3$, reflux, 6 h, 84%; (iii) $LiBH_4$, MeOH, Et_2O, 0°C, 1 h, 80%; (iv) Dess–Martin, CH_2Cl_2, rt, 1 h, 99%; (v) $BH(NMe_4)(OAc)_3$, AcOH, MeCN, −30°C, 18 h, 83%; (vi) TBSOTf, 2,6-lutidine, −78°C, 15 min, 77%; (vii) diethylphosphonoacetic acid, DCC, DMAP, 0°C→rt, 2 h, 86%.

rearrangement, first gave the racemic γ,δ-unsaturated aldehyde **15**. An Evans aldol reaction between **15** and (4*S*,5*R*)-4-methyl-5-phenyl-3-propionyloxazolidin-2-one next led to a 1:1 mixture of the diastereoisomeric imides **16** and **17** in a combined 79% yield (Scheme 3). The diastereoisomers were separated by chromatography, and their stereochemistries followed unambiguously from analysis of relevant coupling data in the NMR spectra of the corresponding δ-lactones, **18** and **19**, produced from them,[15] viz. J_{vic} 7 and 6 Hz for **18**; J_{vic} 11 and 6 Hz for **19**.

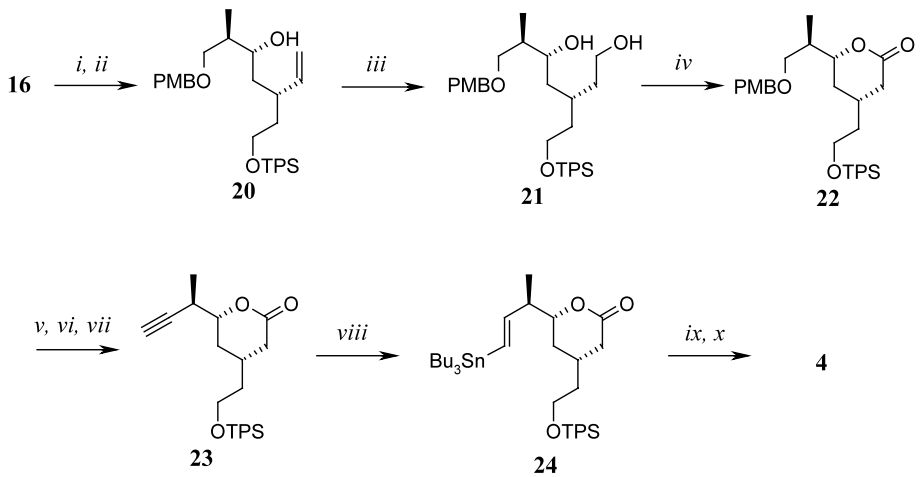
The diastereoisomer **16**, with the 'correct' stereochemistry for rhizoxin, was next reduced with $LiBH_4$ leading to the corresponding primary alcohol, which was then protected as its PMB ether **20**. A straightforward hydroboration–oxidation procedure converted the alkene **20** into the 1,5-diol **21**, which was then oxidised to the δ-lactone **22**. Deprotection of the PMB group in **22** followed by Dess–Martin oxidation of the resulting primary alcohol next produced an aldehyde which underwent a smooth reaction with dimethyl diazomethylphosphonate[16] leading to the terminal acetylene **23**. The acetylene **23** was converted into the *E*-vinyl stannane **24**[17] which was then deprotected, followed by oxidation, leading to the aldehyde vinyl stannane **4** (Scheme 4).

Interestingly, the diastereoisomer **17**, with the 'incorrect' stereochemistry for rhizoxin, could also be converted into the same 1,5-diol intermediate **21** by the series of reactions described in Scheme 5, thereby allowing recycling of this easily available precursor.

A Wadsworth–Emmons olefination reaction between the phosphonate **3** and the aldehyde **4**, under Masamune–Roush conditions,[18] led exclusively to the *E*-alkene **25** in a pleasing 74% yield. When this stannane–iodide **25** was treated with $AsPh_3$–Pd(0) dibenzylideneacetone[19] in degassed DMF at 70°C for 5 h, it underwent smooth intramolecular sp^2–sp^2 cross-coupling with preservation of the double bond



Scheme 3. *Reagents and conditions*: (i) DIBAL-H, THF, −78°C, 1 h, 93%; (ii) $EtOCH{=}CH_2$, $Hg(O_2CCF_3)_2$, rt, 8 h, 78%; (iii) 170°C, sealed tube, 36 h, 97%; (iv) Bu_2BOTf, Et_3N, (4*S*,5*R*)-5-methyl-4-phenyl-3-propionyloxazolidin-2-one, CH_2Cl_2, −78°C→0°C, 2 h, 79%.

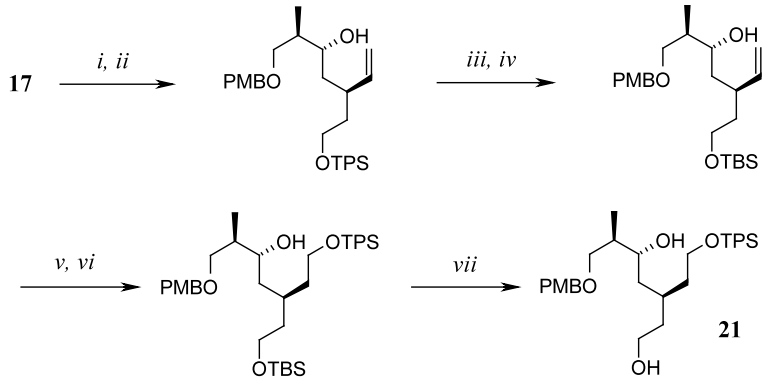


Scheme 4. *Reagents and conditions*: (i) $LiBH_4$, MeOH, Et_2O, 0°C, 2 h, 70%; (ii) $PMBO(N{=}H)CCl_3$, CSA, CH_2Cl_2, −20°C→0°C, 72 h, 60%; (iii) 9-BBN-H, 0°C→rt, 12 h, then NaOH, H_2O_2, 0°C, 4 h, 91%; (iv) Ag_2CO_3/Celite, PhH, reflux, 3 h, 91%; (v) DDQ, CH_2Cl_2, rt, 2 h, 100%; (vi) Dess–Martin, CH_2Cl_2, rt, 1 h, 84%; (vii) $(MeO)_2(O)PCHN_2$, KO′Bu, THF, −78°C, 2 h, 100%; (viii) NBS, $AgNO_3$, acetone, 1 h, then $Pd(PPh_3)_4$, Bu_3SnH, THF, rt, 3 h, 70%; (ix) TBAF, TsOH, THF, rt, 3 h, 70%; (x) Dess–Martin, pyr, CH_2Cl_2, rt, 1 h, 70%.

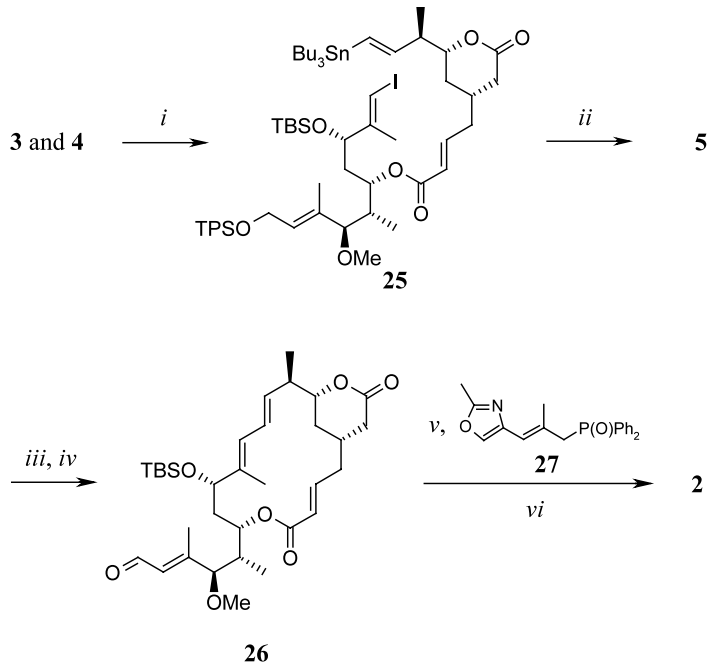
geometries in the precursor leading to the 16-membered macrocyclic lactone core **5** in rhizoxin in an acceptable 48% yield (Scheme 6). Selective removal of the primary TBDPS protecting group in **5**, followed by oxidation of the resulting allylic alcohol with MnO_2 next gave the α,β-unsaturated aldehyde **26**. A Horner olefination reaction between **26** and the oxazole substituted phosphine oxide **27**, at −78°C in the presence of KHMDS, next led to the all *E*-conjugated triene,[20] which on deprotection with HF/pyridine produced (+)-rhizoxin D **2** as a solid. The synthetic rhizoxin showed chiroptic and NMR spectroscopic data which were identical to those reported for the natural product.[4]

Acknowledgements

We thank Merck Sharp and Dohme (studentship to I.S.M.) and the E.P.S.R.C. together with Aventis (studentship to J.P.S.) for support. We also thank Dr. D. A. Entwistle for modelling the key Stille reaction and G. Rescourscino for synthesising the phosphine oxide



Scheme 5. *Reagents and conditions*: (i) $LiBH_4$, MeOH, Et_2O, 0°C, 2 h, 96%; (ii) PMBO(N=H)CCl_3, CSA, CH_2Cl_2, −20°C→0°C, 72 h, 62%; (iii) TBAF, THF, rt, 2 h, 99%; (iv) TBSCl, Imid., CH_2Cl_2, rt, 2 h, 82%; (v) 9-BBN-H, 0°C→rt, 12 h, then NaOH, H_2O_2, 0°C, 4 h, 95%; (vi) TBDPSCl, Imid., CH_2Cl_2, rt, 2 h, 96%; (vii) PPTS, EtOH, 60°C, 2 h, 72%.



Scheme 6. *Reagents and conditions*: (i) LiCl, DBU, MeCN, 0°C→rt, 1 h, 74%; (ii) Pd_2dba_3, $AsPh_3$, DMF, 70°C, 5 h, 48%; (iii) TBAF/AcOH (1:1), THF, rt, 8 h, 74%; (iv) MnO_2, CH_2Cl_2, rt, 3 h, 100%; (v) KHMDS, THF, −78°C→0°C, 1 h, 38%; (vi) HF/Pyr, pyr, THF, rt, 48 h, 78%.

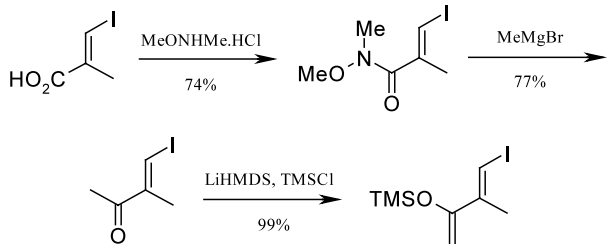
27. Finally, we thank Professor David Williams for helpful correspondence and for provision of NMR spectroscopic data for his synthetic rhizoxin D.

References

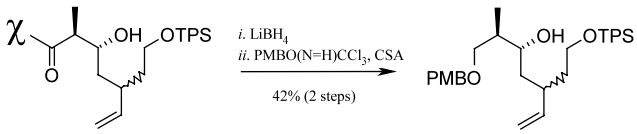
1. (a) Iwasaka, S.; Kobayashi, H.; Furukawa, J.; Namikoshi, M.; Okuda, S. *J. Antibiot*. **1984**, *37*, 354; (b) Iwasaka, S.; Namikoshi, M.; Kobayashi, H.; Furukawa, J.; Okuda, S.; Itai, A.; Kasuya, A.; Iitaka, Y.; Sato, Z. *J. Antibiot*. **1986**, *39*, 424.
2. Kiyoto, S.; Kawai, Y.; Kawakita, T.; Kiuo, E.; Okuhara, M.; Uchida, I.; Tanaka, H.; Hashimoto, M.; Terano, H.; Kohsaka, M.; Aoki, H.; Imanaka, H. *J. Antibiot*. **1986**, *39*, 762.
3. McLeod, H. L.; Murray, L. S.; Wanders, J.; Setanoians, A.; Graham, M. A.; Pavlidis, N.; Heinrich, B.; Huinink, W. W. T.; Wagenerm, D. J. T.; Aamdal, S.; Verweij, J. *Br. J. Cancer* **1996**, *74*, 1944 and references cited therein.
4. Iwasaka, S.; Namikoshi, M.; Kobayashi, H.; Furukawa, J.; Okuda, S. *Chem. Pharm. Bull*. **1986**, *34*, 1387.
5. Synthetic approaches: (a) Rama Rao, A. V.; Sharma, G. V. M.; Bhanu, M. N. *Tetrahedron Lett*. **1992**, *33*, 3907; Rama Rao, A. V.; Bhanu, M. N.; Sharma, G. V. M. *Tetrahedron Lett*. **1993**, *34*, 707; (c) Keck, G. E.; Park, M.; Krishnamurthy, D. J. *J. Org. Chem*. **1993**, *58*, 3787; Keck, G. E.; Savin, K. A.; Weglarz, M. A.; Cressman, E. N. K. *Tetrahedron Lett*. **1996**, *37*, 3291; (c) Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett*. **1995**, *36*, 6029; Provencal, D. P.; Gardelli, C.; Lafontaine, J. A.; Leahy, J. W. *Tetrahedron Lett*. **1995**, *36*, 6033; (d) White, J. D.;

Nylund, C. S.; Green, N. J. *Tetrahedron Lett*. **1997**, *38*, 7329; White, J. D.; Holoboski, M. A.; Green, N. J. *Tetrahedron Lett*. **1997**, *38*, 7333; (e) Burke, S. D.; Hong, J.; Mongin, A. P. *Tetrahedron Lett*. **1998**, *39*, 2239; Burke, S. D.; Hong, J.; Lennox, J. R.; Mongin, A. P. *J. Org. Chem*. **1998**, *63*, 6952; (f) Davenport, R. J.; Regan, A. C. *Tetrahedron Lett*. **2000**, *41*, 7619; (g) N'Zoutani, M. A.; Pancrazi, A.; Ardisson, J. *Synlett* **2001**, *6*, 769.

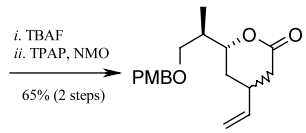
6. Total synthesis of rhizoxin A: (a) Nakada, M.; Kobayashi, S.; Iwasaka, S.; Ohno, M. *Tetrahedron Lett*. **1993**, *34*, 1035; (b) Nakada, M.; Kobayashi, S.; Shibasaki, M.; Iwasaka, S.; Ohno, M. *Tetrahedron Lett*. **1993**, *34*, 1039.
7. Total synthesis of rhizoxin D: (a) Kende, A. S.; Blass, B. E.; Henry, J. R. *Tetrahedron Lett*. **1995**, *36*, 4741; (b) Williams, D. R.; Werner, K. M.; Feng, B. *Tetrahedron Lett*. **1997**, *38*, 6825; (c) Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *Tetrahedron Lett*. **1999**, *40*, 4145; (d) Keck, G. E.; Wager, C. A.; Wager, T. T.; Savin, K. A.; Covel, J. A.; McClaws, M. D.; Krishnamurthy, D.; Cee, V. J. *Angew. Chem., Int. Ed. Engl*. **2001**, *40*, 231.
8. (a) Gage, J. R.; Evans, D. A. *Org. Synth*. **1989**, *68*, 88; (b) Gage, J. R.; Evans, D. A. *Org. Synth*. **1989**, *68*, 83.
9. Corey, E. J.; Bock, M. G.; Kosikowski, A. P.; Rama Rao, A. V.; Floyd, D.; Lipschutz, B. *Tetrahedron Lett*. **1978**, *19*, 1051.
10. The synthesis of the silyl enol ether 10, was achieved from 3-iodo-2-methylprop-2-enoic acid as follows:



11. Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett*. **1999**, *40*, 4457.
12. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G.; Livingstone, A. B. *J. Am. Chem. Soc*. **1995**, *117*, 6619.
13. (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett*. **1986**, *27*, 5939; (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc*. **1988**, *110*, 3560.
14. Nacro, K.; Baltas, M.; Gorrichon, L. *Tetrahedron* **1999**, *55*, 14013.
15. The δ-lactones **18** and **19** were synthesised from the corresponding diastereomeric aldol isomers, **16** and **17**, respectively, following the four-step procedure summarised below:



16 and **17** χ = Evans' auxiliary



18 and **19**

16. Seyforth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem*. **1978**, *43*, 1011.
17. (a) Boden, C. D. J.; Pattenden, G.; Ye, T. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2417; (b) Zhang, H. X.; Guibé, F.; Balavoine, G. *J. Org. Chem*. **1990**, *55*, 1857.
18. Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett*. **1984**, *32*, 2183.
19. Farina, V.; Krishnan, B. *J. Am. Chem. Soc*. **1991**, *113*, 9585.
20. As reported by Williams and co-workers,[7b] on a small scale, hydrolytic opening of the δ-lactone in **26** is observed during the olefination reaction. In practice, the crude mixture was subjected to a Yamaguchi esterification (procedure: Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc*. **1986**, *108*, 5221) prior to purification, as recommended by Williams et al.