Diterpenes

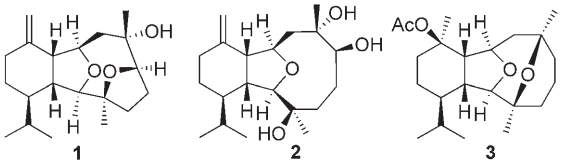
DOI: 10.1002/anie.200704678

Asymmetric Total Synthesis and X-Ray Crystal Structure of the Cytotoxic Marine Diterpene (+)-Vigulariol**

*Jochen Becker, Klaus Bergander, Roland Fröhlich, and Dieter Hoppe**

Dedicated to Professor Larry E. Overman on the occasion of his 65th birthday.

(+)-Vigulariol (**1**) is a cytotoxic, tetracyclic diterpene which has been isolated from the sea pen *Vigularia juncea*.[1] It



belongs to the impressively large class of the cladiellin (eunicellin) diterpenes, of which many bear interesting biological activities.[2] (+)-**1** has shown to exhibit cyctotoxity against A 549 (human lung adenocarcinoma) cell culture at an IC_{50} of 18.33 μg mL^{-1}.[1] Two other soft-coral diterpenes sclerophytin A (**2**)[3,4] and polyanthellin A (**3**)[5,6] have shown high cytotoxicity and antimalarial activity, respectively. Their attractive molecular architectures and their diverse biological activities previously led to several ingenious total syntheses of some members of this natural product family by the research groups of Paquette,[3a,c] Overman,[3b,c,7] Crimmins,[8] and Kim.[5]

(+)-**1** was formed as a by-product during Paquette and co-workers' synthesis of **2** before it was known to be natural product and was therefore not fully characterized.[3a] The total synthesis of *rac*-**1** over 20 linear steps was quite recently published by Clark et al.[9] Herein we present a short and efficient total synthesis and, in addition, the solid-state structure of enantiomerically pure (+)-vigulariol (**1**), by applying our previous synthetic and mechanistic investigations.[10,11]

[*] J. Becker, Dr. K. Bergander,[+] Dr. R. Fröhlich,[$] Prof. Dr. D. Hoppe
Organisch-Chemisches Institut
Westfälische Wilhelms-Universität Münster
Corrensstraße 40, 48149 Münster (Germany)
Fax: (+49) 251-83-36531
E-mail: dhoppe@uni-muenster.de
Homepage: http://www.uni-muenster.de/Chemie.oc/research/hop/hoppe.html

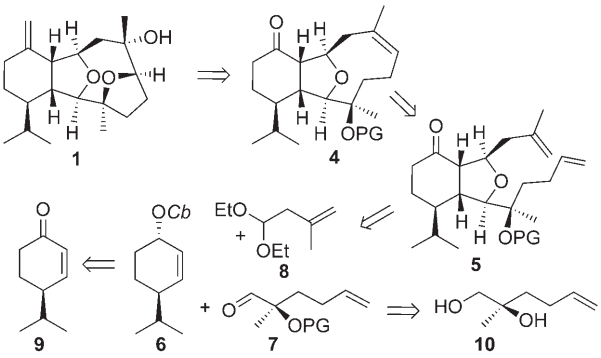
[+] NMR experiments

[$] X-Ray crystal structure analysis

[**] This work was supported by the Deutsche Forschungsgemeinschaft (SFB 424) and the Fonds der Chemischen Industrie (grant for J.B.). We thank M. Renger, K. Gottschalk, and D. Hog for their skilful experimental contributions.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

As depicted in Scheme 1, (+)-vigulariol (**1**) could be elaborated by stereoselective epoxidation of the C=C double bond of tricycle **4**. Deprotection of the hydroxy group was

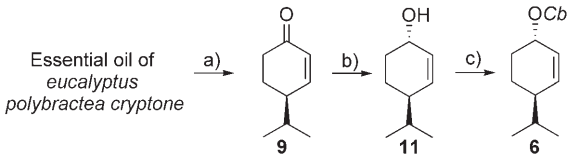


Scheme 1. Retrosynthetic analysis of (+)-vigulariol (**1**). *Cb* = C(O)N*i*Pr$_2$, PG = protecting group.

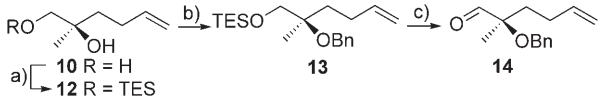
envisaged to lead to subsequent intramolecular nucleophilic ring-opening of the oxirane, followed by the introduction of the exocyclic methylene group. Our convergent strategy for the construction of tricycle **4** centered around three key reactions: the asymmetric homoaldol reaction[12] of carbamate **6**[10b] with α-stereogenic enal **7**, followed by Krämer THF synthesis[13] with acetal **8**,[14] and ring-closing metathesis[15] of the diene **5**. (*R*)-4-Isopropylcyclohex-2-enone (**9**) [(*R*)-(−)-cryptone)][16] was chosen as starting material for the synthesis of **6**. Known enantiopure diol **10**[17] was identified for the construction of **7**.

Several enantioselective syntheses of (*R*)-**9** are known,[16] and we applied the methodology of Fuchs et al.[18] to obtain (*R*)-**9** with 99% *ee* (4 steps, 60–66% yield). But, as we became aware that commercial eucalyptus oil contains approximately 5% of the cyclohexenone **9**,[19,20] we developed the following approach: The oil was subjected to chromatography, yielding a mixture of (*R*)-**9** with 97% *ee* (HPLC) and a sesquiterpene bearing no carbonyl function. The mixture was reduced with $LiAlH_4$ to yield cycloalkenol **11**[21] (d.r. = 84:16), which was separated from the sesquiterpene by simple chromatography on silica gel (Scheme 2). Carbamoylation of **11** and separation of the diastereomers yielded (1*S*,4*R*)-**6**[10b] (97% *ee*).

As it is known that a direct oxidation of silyl ethers to the corresponding aldehydes is possible,[22] enantiomerically pure diol **10** was quantitatively transferred into the triethylsilyl ether **12**. *O*-Benzyl protection of **12**,[23] followed by Swern oxidation[24] provided the required enal **14** in 69% yield over three steps (Scheme 3).

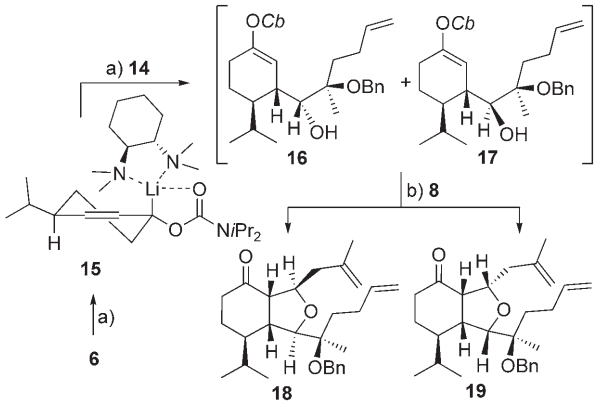


Scheme 2. Preparation of carbamate **6**. Reagents and conditions: a) Flash column chromatography (FCC), 12.6 g **9** (97% *ee*): C15-sesquiterpene in a ratio of 47:53 (GC) from essential oil (100 mL); b) 1.2 equiv $LiAlH_4$, Et_2O, −78 °C, 30 min, FCC, 5.27 g (37.6 mmol) **11** (d.r. = 84:16); c) 1.2 equiv NaH, 1.4 equiv $iPr_2NC(O)Cl$, THF, reflux, 12 h, FCC, 78% **6** (97% *ee*), 12% *cis*-**6**.



Scheme 3. Synthesis of chiral aldehyde **14**. Reagents and conditions: a) 1.05 equiv TESCl, 2.0 equiv imidazole, DMF, 0 °C to 22 °C, 1.5 h, 99%; b) 2.5 equiv benzyl 2,2,2-trichloroacetimidate, 0.28 equiv F_3CSO_3H, Et_2O, 0 °C to 22 °C, 2.25 h, 86%; c) 1) 10.0 equiv DMSO, 5.0 equiv $(COCl)_2$, −60 °C, 14 h, 2) 20.0 equiv DIPEA, 22 °C, 45 min, 81%. TES = triethylsilyl, Bn = benzyl, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, DIPEA = diisopropylethylamine.

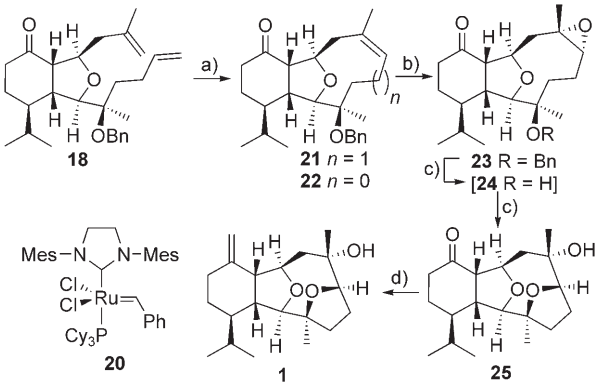
After stereospecific deprotonation of **6** (*s*BuLi, *rac-trans*-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane (TMCDA)),[10a] lithium–titanium exchange of the lithiated species **15** was accomplished with $ClTi(OiPr)_3$ (Scheme 4).[25]



Scheme 4. Synthesis of the metathesis precursor **18** by a homoaldol reaction and THF cyclocondensation. Reagents and conditions: a) 1) 1.05 equiv *s*BuLi/TMCDA, Et_2O, −78 °C, 2 h; 2) 1.74 equiv $ClTi(OiPr)_3$ (1.74 M in toluene), −78 °C, 2 h; 3) 2.5 equiv **14**, −78 °C to 22 °C, 13.5 h, **16**/**17** (d.r. = 83:17, 40% from **6**), 69% **14** reisolated; b) 2.1 equiv **8**, 1.9 equiv $BF_3{\cdot}OEt_2$, Et_2O, 0 °C, 35 min; 71% **18**, 13% **19** (from **16**/**17** 83:17). TMCDA = *rac-trans*-*N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminocyclohexane.

The inversion of the configuration in the transmetallation step is supported by the steric shielding of the 4-isopropyl group. Addition of aldehyde **14** led to two inseparable diastereomeric homoaldol products **16** and **17** (yield 40%, d.r. = 83:17).[26] A mixture of **16** and **17** (83:17) was subjected to BF_3-mediated condensation[13] with acetal **8** to provide the separable hexahydroisobenzofuran-4(1*H*)-ones **18** (71%) and **19** (13%). ^1H NMR nOesy analysis indicated that the desired isomer **18** was the major product.[27]

Although it was reported by Crimmins et al.[28] that oxacyclononenes are accessible by ring-closing metathesis, the cyclisation of **18** seemed to be critical, because the reported attempts of Overman and Joe[29] and Jung and Pontillo[30] to construct bi- and tricycles similar to **21** by metathesis failed. Grubbs 1 and Hoveyda's catalyst did not lead to the formation of **21**. However, the Grubbs 2 catalyst **20**[31] in refluxing benzene yielded **21** (45%) along with the oxacyclooctene **22** (17%) (Scheme 5).



Scheme 5. Metathesis and completion of the total synthesis of (+)-vigulariol (**1**). Reagents and conditions: a) **20** (10 mol%), benzene, reflux, 1.3 h, 45% **21**, 17% **22**; b) 1.1 equiv DMDO, acetone, −20 °C, 30 min, 81% **23**, 9% α-**23**; c) 10% Pd/C (20 mol%), H_2 (1 bar), EtOAc, 22 °C, 1.25 h, 91%; d) 4.0 equiv Ph_3PCH_3Br, 3.5 equiv NaHMDS (1 M in THF), toluene, 80 °C, 45 min, 93%. DMDO = dimethyldioxirane, NaHMDS = sodium hexamethyldisilazide, Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.

Cycloalkene **21** was subjected to epoxidation by means of dimethyldioxirane (DMDO)[32] to form oxirane **23** (β: 81% yield, α: 9% yield). As expected, the less shielded β-face is preferentially attacked. Hydrogenolytic *O*-debenzylation of **23** proceeded smoothly, and the bis(tetrahydrofuran) **25** was isolated in 91% yield. The intermediate alcohol **24** underwent rapid stereospecific attack onto the oxirane moiety. Finally, introduction of the exocyclic methylene group by Wittig olefination[33] provided the target molecule (+)-**1** in essentially quantitative yield.

The NMR and nOe data and the specific optical rotation ($[\alpha]_D^{20} = +4.2$ ($c = 0.24$, $CHCl_3$), reported[1] $[\alpha]_D^{27} = +3.6$ ($c = 0.24$, $CHCl_3$)) of our sample of (+)-**1** match well with reported data.[1,9] Surprisingly, the compound we obtained was crystalline (m.p. = 141.7 °C), whereas natural vigulariol (+)-**1** was reported to be a colorless oil.[1] For this reason, we undertook an X-ray crystal structure analysis, which confirmed the correct constitution and configuration of the synthetic sample of (+)-**1** (Figure 1).[34–36]

In summary, we have developed a short synthetic route for (+)-vigulariol (**1**), which is based on the asymmetric homoaldol reaction of **6** and subsequent THF cyclisation of **16**, starting from simple enantiomerically pure starting materials. We have also shown that the tricyclic core of the cladiellins is

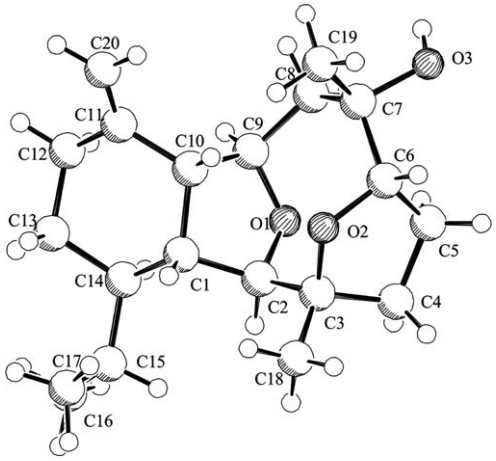


Figure 1. Solid-state structure of (+)-**1**.[34–36]

achievable by ring-closing metathesis of dialkenyl tetrahydrofuran **18**. As the keto function of key intermediate **21** allows several transformations, many of these soft-coral diterpenes, for example **3**, are considered to be accessible by slight variations of this method.

Received: October 10, 2007
Published online: January 22, 2008

Keywords: asymmetric synthesis · carbamates · homoaldol reactions · metathesis · total synthesis

[1] J.-H. Su, H.-C. Huang, C.-H. Chao, L.-Y. Yan, Y.-C. Wu, J.-H. Sheu, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 877–879.
[2] Reviews: a) P. Bernardelli, L. A. Paquette, *Heterocycles* **1998**, *49*, 531–556; b) P.-S. Sung, M.-C. Chen, *Heterocycles* **2002**, *57*, 1705–1715.
[3] Total synthesis: a) P. Bernardelli, O. M. Moradei, D. Friedrich, J. Yang, F. Gallou, B. P. Dyck, R. W. Doskotch, T. Lange, L. A. Paquette, *J. Am. Chem. Soc.* **2001**, *123*, 9021–9032; b) D. W. C. MacMillan, L. E. Overman, L. D. Pennington, *J. Am. Chem. Soc.* **2001**, *123*, 9033–9044; c) F. Gallou, D. W. C. MacMillan, L. E. Overman, L. A. Paquette, L. D. Pennington, J. Yang, *Org. Lett.* **2001**, *3*, 135–137.
[4] Isolation and cytotoxicity: a) P. Sharma, M. Alam, *J. Chem. Soc. Perkin Trans. 1* **1988**, 2537–2540; b) M. Alam, P. Sharma, A. S. Zektzer, G. E. Martin, X. Ji, D. J. van der Helm, *J. Org. Chem.* **1989**, *54*, 1896–1900.
[5] Total synthesis: H. Kim, H. Lee, J. Kim, S. Kim, D. Kim, *J. Am. Chem. Soc.* **2006**, *128*, 15851–15855.
[6] Isolation and biological activity: C. A. Ospina, A. D. Rodríguez, E. Ortega-Barria, T. L. Capson, *J. Nat. Prod.* **2003**, *66*, 357–363.
[7] The first synthesis of an eunicelline: a) D. W. C. MacMillan, L. E. Overman, *J. Am. Chem. Soc.* **1995**, *117*, 10391–10392; Review: b) L. E. Overman, L. D. Pennington, *J. Org. Chem.* **2003**, *68*, 7143–7157.
[8] M. T. Crimmins, B. H. Brown, H. R. Plake, *J. Am. Chem. Soc.* **2006**, *128*, 1371–1378.
[9] J. S. Clark, S. T. Hayes, C. Wilson, L. Gobbi, *Angew. Chem.* **2007**, *119*, 441–444; *Angew. Chem. Int. Ed.* **2007**, *46*, 437–440.
[10] a) J. Becker, S. Grimme, R. Fröhlich, D. Hoppe, *Angew. Chem.* **2007**, *119*, 1672–1676; *Angew. Chem. Int. Ed.* **2007**, *46*, 1645–1649; b) J. Becker, R. Fröhlich, O. Kataeva, D. Hoppe, *Eur. J. Org. Chem.* **2007**, 3349–3364.
[11] For a recent application in the synthesis of precursors for eleuterobin, see: S. Dhulut, A. Bourin, M.-I. Lannou, E. Fleury, N. Lensen, E. Chelain, A. Pancrazi, J. Ardisson, J. Fahy, *Eur. J. Org. Chem.* **2007**, 5235–5243.
[12] For reviews, see: a) D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376–2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282–2316; b) D. Hoppe, F. Marr, M. Brüggemann, *Top. Organomet. Chem.* **2003**, *5*, 61–138; c) P. Beak, T. A. Johnson, D. D. Kim, S. H. Lim, *Top. Organomet. Chem.* **2003**, *5*, 139–176; d) D. Hoppe, G. Christoph in *The Chemistry of Organolithium Compounds*, *Vol. 2* (Eds.: Z. Rappoport, I. Marek), Wiley, Chichester, **2004**, pp. 1055–1164; e) Review of organolithium compounds in total synthesis: R. Chinchilla, C. Nájera, M. Yus, *Tetrahedron* **2005**, *61*, 3139–3176; f) For a recent application of discodermolide in total synthesis, see: E. de Lemos, F.-H. Porée, A. Commerçon, J.-F. Betzer, A. Pancrazi, J. Ardisson, *Angew. Chem.* **2007**, *119*, 1949–1953; *Angew. Chem. Int. Ed.* **2007**, *46*, 1917–1921.
[13] a) D. Hoppe, T. Krämer, C. Freire Erdbrügger, E. Egert, *Tetrahedron Lett.* **1989**, *30*, 1233–1236; b) H. Paulsen, C. Graeve, R. Fröhlich, D. Hoppe, *Synthesis* **1996**, 145–148; c) S. Ünaldi, M. Özlügedik, R. Fröhlich, D. Hoppe, *Adv. Synth. Catal.* **2005**, *347*, 1621–1626.
[14] J. W. Cornforth, M. E. Firth, *J. Chem. Soc.* **1958**, 1091–1099.
[15] For reviews, see: a) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; b) T. M. Trnka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29.
[16] K. Mori, *Tetrahedron: Asymmetry* **2006**, *17*, 2133–2142.
[17] M. E. Kuehne, W. G. Bornmann, I. Markó, Y. Qin, K. L. LeBoulluec, D. A. Frasier, F. Xu, T. Mulamba, C. L. Ensinger, L. S. Borman, A. E. Huot, C. Exon, F. T. Bizzarro, J. B. Cheung, S. L. Bane, *Org. Biomol. Chem.* **2003**, *1*, 2120–2136.
[18] J. Evarts, E. Torres, P. L. Fuchs, *J. Am. Chem. Soc.* **2002**, *124*, 11093–11101.
[19] D. J. King, R. M. Gleadow, I. E. Woodrow, *New Phytol.* **2006**, *172*, 440–451.
[20] *Eucalyptus polybractea cryptone* was purchased from Martina Braun Naturprodukte, Ottersweiher, Germany; see: www.osh-adhi.de.
[21] J. M. Coxon, G. J. Hydes, P. J. Steel, *Tetrahedron* **1985**, *41*, 5213–5217.
[22] G. A. Tolstikov, M. S. Miftakov, M. E. Adler, N. G. Komissarova, O. M. Kuznetsov, N. S. Vostrikov, *Synthesis* **1989**, 940–942.
[23] H.-P. Wessel, T. Iversen, T. R. Bundle, *J. Chem. Soc. Perkin Trans. 1* **1985**, 2247–2250.
[24] A. J. Mancuso, D. Swern, *Synthesis* **1981**, 165–185.
[25] Reviews: a) B. Weidmann, D. Seebach, *Angew. Chem.* **1983**, *95*, 12–26; *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 31–45; b) M. T. Reetz in *Organometallics in Synthesis*, 2nd ed. (Ed: M. Schlosser), Wiley-VCH, Chichester, **2002**, pp. 817–923.
[26] A discussion of the transition states of the homoaldol reaction can be found in ref. [10b]. The configurations of the products **16** and **17** were established by nOesy studies after conversion to the THF derivatives **18** and **19**.
[27] For nOesy correlatons of **18** and **19**, see the Supporting Information. Homoaldol products that are *syn*-configured like **17** lead to an *all-cis*-substitution pattern of the THF, see: J. Becker, R. Fröhlich, K. Salorinne, D. Hoppe, *Eur. J. Org. Chem.* **2007**, 3337–3348.
[28] a) M. T. Crimmins, K. A. Emmitte, *J. Am. Chem. Soc.* **2001**, *123*, 1533–1534; b) M. T. Crimmins, K. A. Emmitte, A. L. Choy, *Tetrahedron* **2002**, *58*, 1817–1834; c) M. T. Crimmins, M. T. Powell, *J. Am. Chem. Soc.* **2003**, *125*, 7592–7595.
[29] The ring-closing proceeded with loss of a methylene group: D. Joe, L. E. Overman, *Tetrahedron Lett.* **1997**, *38*, 8635–8638.

[30] M. E. Jung, J. Pontillo, *Tetrahedron* **2003**, *59*, 2729 – 2736.
[31] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953 – 956.
[32] R. W. Murray, M. Singh, *Organic Synthesis Coll. Vol. 9*, **1998**, 288; R. W. Murray, M. Singh, *Organic Synthesis Coll. Vol. 74*, **1997**, 91.
[33] G. Wittig, U. Schöllkopf, *Chem. Ber.* **1954**, *87*, 1318 – 1330.
[34] The absolute configuration of the starting material (*R*)-**9** was proven by X-ray crystallography with anomalous dispersion of a corresponding THF; see ref. [10b].
[35] X-ray crystal structure analysis for (+)-**1**: $C_{20}H_{32}O_3$, $M_r = 320.46$, colorless crystal $0.20 \times 0.08 \times 0.08$ mm^3, $a = 9.0189(1)$, $b = 10.6042(1)$, $c = 9.7714(1)$ Å, $\beta = 97.051(1)°$, $V = 927.45(2)$ Å^3, $\rho_{calc} = 1.148$ g cm^{-3}, $\mu = 0.589$ mm^{-1}, empirical absorption correction ($0.891 \le T \le 0.954$), $Z = 2$, monoclinic, space group $P2_1$ (No. 4), $\lambda = 1.54178$ Å, $T = 223$ K, ω and ϕ scans, 5758 reflections collected ($\pm h$, $\pm k$, $\pm l$), $[(\sin\theta)/\lambda] = 0.60$ Å^{-1}, 2252 independent ($R_{int} = 0.079$) and 2049 observed reflections [$I \ge 2\sigma(I)$], 213 refined parameters, $R = 0.058$, $wR^2 = 0.161$, Flack parameter 0.1(4), max. residual electron density 0.23 (−0.20) e Å^{-3}, hydrogen atoms calculated and refined as riding atoms.
[36] The data set was collected with a Nonius KappaCCD diffractometer. Programs used: data collection COLLECT (Nonius B.V., **1998**), data reduction Denzo-SMN (Z. Otwinowski, W. Minor, *Methods Enzymol.* **1997**, *276*, 307 – 326), absorption correction Denzo (Z. Otwinowski, D. Borek, W. Majewski, W. Minor, *Acta Crystallogr. Sect. A* **2003**, *59*, 228 – 234), structure solution SHELXS-97 (G. M. Sheldrick, *Acta Crystallogr. Sect. A* **1990**, *46*, 467 – 473), structure refinement SHELXL-97 (G. M. Sheldrick, Universität Göttingen, **1997**), graphics SCHAKAL (E. Keller, Universität Freiburg, **1997**). CCDC-663250 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.

