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Asymmetric Morita–Baylis–Hillman reaction of chiral glyoxylates

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Abstract—The first Morita–Baylis–Hillman reaction of chiral glyoxylic acid derivatives, i.e. *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam and (−)-8-phenylmenthyl glyoxylate is described. The reaction with cyclic α,β-unsaturated ketones proceeded under the catalytic influence of dimethyl sulfide in the presence of titanium tetrachloride. The adducts were obtained with very high diastereoisomeric excess (over 95% d.e.) and typical yields of 78%. The absolute configuration of the newly created stereogenic center was established by X-ray crystallographic analysis.

1. Introduction

The Morita–Baylis–Hillman reaction (although usually referred to as the Baylis–Hillman reaction, the first reports on this transformation were published by Morita) is a very useful method for C–C bond formation by coupling activated alkenes and carbon electrophiles such as aldehydes or ketones.[1] Apart from ethyl acrylate and acrylonitrile, initially used in this reaction, a variety of other olefins undergo this coupling, such as α,β-unsaturated aldehydes and ketones (both cyclic and acyclic), vinyl sulfoxides and sulfones. Not only simple and substituted aliphatic and aromatic aldehydes can be used as the electrophile but also α-halo ketones, α-keto esters, α-keto lactones and even imines bearing electronegative substituents on the nitrogen atom. The product of the Morita–Bayliss–Hillman reaction contains several functionalities: hydroxy groups, a double bond and alkene and electrophile activating groups and as such, these products can serve as substrates in further transformations. The tertiary amine DABCO reaction originally catalyzed the reaction, however under these conditions it is usually very slow and requires days (or even weeks) to reach completion. Efforts to overcome this obstacle by changing the catalyst to other tertiary amines or tertiary phosphines and/or reaction conditions have resulted only in partial success. Recently, Kataoka et al. introduced a new catalyst system, in which dimethyl sulfide (as well as other sulfides and selenides) in the presence of titanium tetrachloride catalyze the Morita–Baylis–Hillman reaction very efficiently. The reaction is complete within hours.[2]

Numerous attempts have been made to obtain optically active products. This was achieved by the use of chiral olefins, mostly derivatives of acrylic acid carrying chiral auxiliary like 8-phenylmenthol[3] or Oppolzer's sultam.[4] Enantiomerically pure substituted aldehydes including α-branched aldehydes[5] or chiral catalysts have been also applied.[6,7] Due to our continuous interest in the diastereoselective reactions of optically active derivatives of glyoxylic acid,[8–12] we decided to investigate their use as electrophiles in the asymmetric Morita–Baylis–Hillman reaction. So far only the simplest methyl and ethyl glyoxylates were used as electrophiles in this reaction.[13,14] There are more examples of reactions of α-ketoesters[15–18] but so far, to our best knowledge, there are no reports on the use of chiral glyoxylates as electrophiles.

2. Results

The first example of application of chiral glyoxylate in asymmetric Morita–Baylis–Hillman reaction is presented herein.

Glyoxylates **1** and **2** (Scheme 1) were chosen as the most promising compounds, whose diastereodifferentiation abilities had already been demonstrated in many types of reactions.

These two compounds were reacted with representative alkenes under a variety of conditions.

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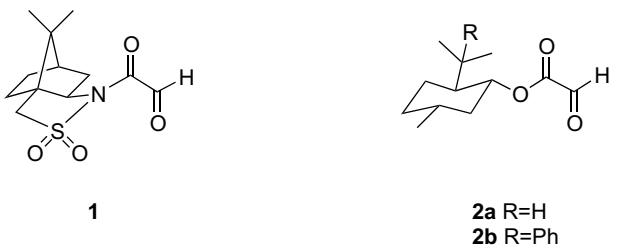
Due to the known susceptibility of *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **1** to the basic conditions, the classical DABCO catalyzed reaction with methyl acrylate led, as expected, to decomposition of **1**. Free chiral auxiliary was recovered from the reaction mixture. Other catalytic systems were then examined. Reactions of methyl acrylate with **1** in the presence of Bu_3P, Bu_3P–Et_2AlCl, and dimethyl sulfide–titanium tetrachloride also led to complex mixtures of products, none of them being Morita–Baylis–Hillman adducts. Similarly, reactions with acyclic (methyl vinyl ketone) and cyclic (2-cyclohexenone) have not given positive results. Obviously, *N*-glyoxyloyl-(2*R*)-bornane-10,2-sultam **1** and products of its reactions are unstable under applied conditions.

We then turned our attention to the glyoxylates **2**, expecting that a typical ester bond would be more stable.

Morita–Baylis–Hillman reaction of (−)-menthyl and (−)-8-phenylmenthyl glyoxylates. Reaction conditions: (i) Me_2S (0.2 equiv.), $TiCl_4$ (1 equiv.), 0°C, CH_2Cl_2. The reaction of readily available (−)-menthyl glyoxylate **2a** with 2-cyclohexenone **3a** was conducted in the presence of 0.2 equiv. of dimethyl sulfide and 1.0 equiv. of titanium tetrachloride, using methylene chloride as solvent (Kataoke conditions). The addition proceeded smoothly at 0°C to give the respective product in 45% isolated yield. Inspection of its ^1H NMR spectrum revealed that the product was a mixture of two diastereoisomers **4a** and **5a** (Scheme 2). Acetylation of the crude product gave the respective acetates, ^1H NMR analysis of which allowed for precise integration of the well-separated signals of both diastereoisomers. As expected, the d.e. with this inefficient auxiliary was low, being only 8.7%. Subsequently, under the same conditions, (−)-8-phenylmenthyl glyoxylate **2b** was reacted with **3a**. After 21 h at 0°C, the reaction product was obtained in 78% isolated yield. Careful analysis of 500 MHz ^1H NMR spectra of both this product and its acetate showed that only single diastereoisomer, **4b**, was produced, thus the d.e. of the reaction can be described as >95%. Similarly, the reaction of **2b** with 2-cyclopentenone **3b** gave, under the same conditions, diastereoisomerically pure adduct **4c** in 76% yield. The absolute stereochemistry of the newly created stereogenic center of compound **4b** was established by X-ray analysis as *S* (Fig. 1). The direction of the asymmetric induction is in good accordance with the model depicted at Scheme 3. Both carbonyl groups of the glyoxylate moiety are in *s-cis* conformations (conformers **A** and **B**), and the phenyl ring shields one of the diastereotopic faces of the reacting formyl group. The simultaneous complexation of both the glyoxylate carbonyl groups and the cyclohexenone oxygen (conformer **B**), as already proposed for ene reaction,[19] can further rigidify the transition state, ensuring *s-cis* disposition of the carbonyl groups. The unfavorable steric interactions between one of the carbonyl groups and dimethylsulfide substituent further diminishes the possibility of *re*-attack on *s-trans* conformer **C**. This results in very high selectivity of *si*-attack from above the plane, leading to a virtually single diastereoisomer. On the basis of the above presented model, we presume, that also in adduct **4c** the (*S*)-configuration was induced.

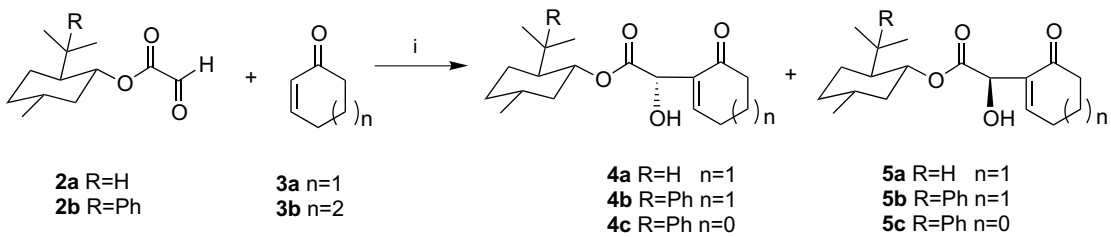


Scheme 1. Potential electrophiles in Morita–Baylis–Hillman reaction.

Encouraged by such excellent results we tried to use another activated olefin as methyl acrylate (we have excluded methyl vinyl ketone from our considerations due to side reactions, observed by us with **1** and by others[2,18]). Surprisingly, no adduct was detected. In further experiments we found that the Me_2S–$TiCl_4$ catalytic system is the only workable choice for this set starting materials. We were not able to obtain any Morita–Baylis–Hillman products in the reaction of **2b** with **3a** catalyzed by DABCO, Bu_3P, and Bu_3P–Et_2AlCl.

3. Conclusions

We have shown that the recently introduced methyl sulfide based catalytic system for the Morita–Baylis–Hillman reaction is the only choice for the reaction of chiral glyoxylates with cyclic α,β-unsaturated ketones. To the best of our knowledge, we have presented here the first example of Morita–Baylis–Hillman reactions of chiral glyoxylates. Respective adducts have been



Scheme 2. Morita–Baylis–Hillman reaction of (−)-menthyl and (−)-8-phenylmenthyl glyoxylates. *Reaction conditions*: (i) Me_2S (0.2 equiv.), $TiCl_4$ (1 equiv.), 0°C, CH_2Cl_2.

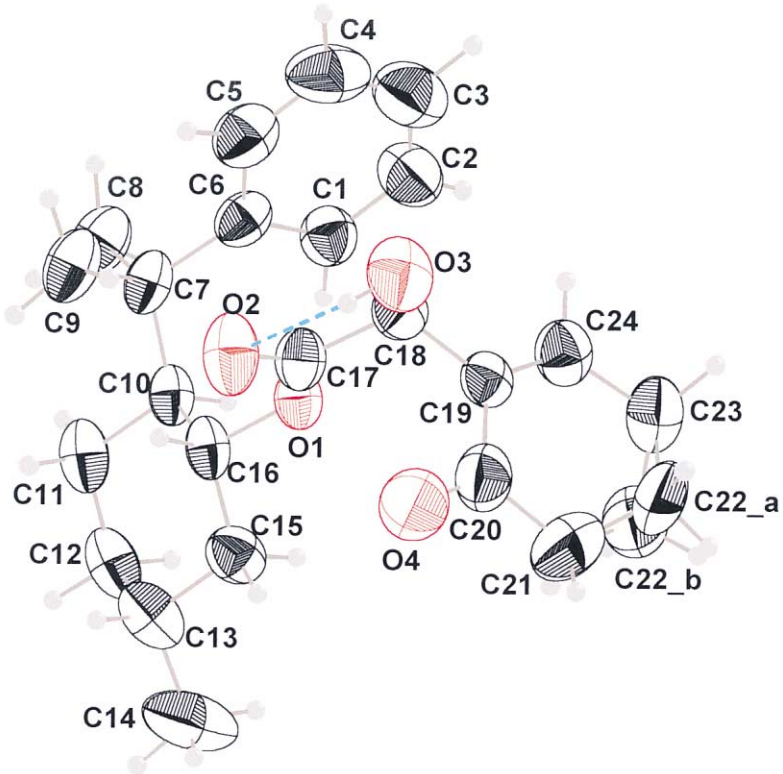
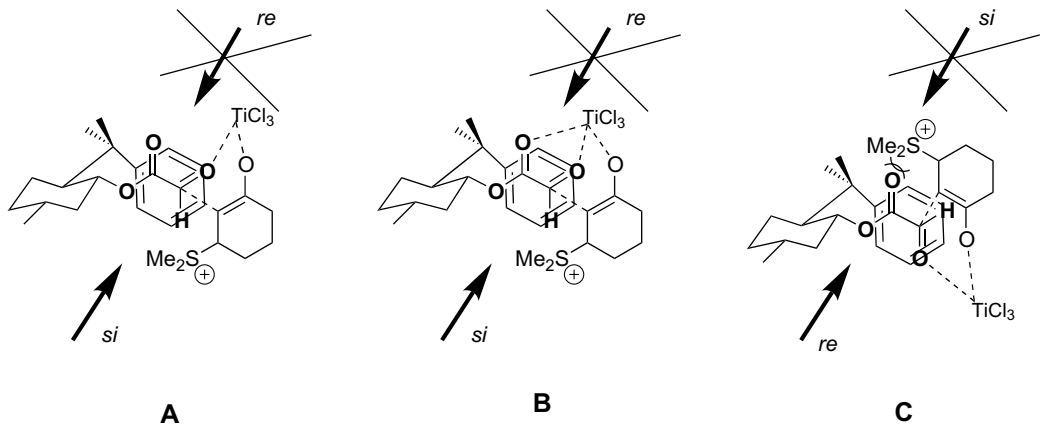


Figure 1. X-Ray crystal structure of **4b**.



Scheme 3. Stereochemical model.

obtained with excellent diastereoselectivity. These multifunctional optically pure compounds are interesting synthons for stereoselective organic synthesis.

4. Experimental

4.1. General

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. Specific rotations were recorded using a Perkin–Elmer PE-241 polarimeter with a thermally jacketed 10 cm cell. IR spectra were obtained on a Perkin–Elmer 1640 FTIR spectrophotometer in KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ using Varian 200 and 500 Unity Plus spectrometers. All chemical shifts are quoted in parts per million relative to tetramethylsilane (δ, 0.00 ppm), and coupling constants (J) are measured in Hertz; (′) denotes signals belonging to the chiral auxiliary and ([a]) or ([b]) to diastereoisomers. Mass spectra were recorded on an AMD-604 Intectra instrument using the EI (electron-impact) technique. All measurements of crystal were performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation. Reactions were carried under argon when necessary. Flash column chromatography was made on silica gel (Kieselgel-60, Merck, 230–400 mesh). *N*-Glyoxyloyl-(2*R*)-bornane-10,2-sultam **1** was obtained according to our own

methodology[20] and (–)-menthyl[21] and (–)-8-phenylmenthyl glyoxylates[19] **2** were obtained according to earlier reported procedures.

4.2. General procedure for Morita–Baylis–Hillman reaction

The glyoxylate (0.5 mmol) was dissolved in CH_2Cl_2 (2.8 ml) in a round bottom flask and cooled to –78°C under an argon atmosphere. To this solution 2-cyclohexen-1-one (0.145 ml, 1.5 mmol, 3 equiv.), methyl sulfide (0.008 ml, 0.1 mmol, 0.2 equiv.) and a solution of $TiCl_4$ in CH_2Cl_2 (1 M, 0.5 ml, 0.5 mmol, 1 equiv.) were added. The mixture was stirred for 21 h at 0°C. The reaction was finally quenched by addition of solid NH_4Cl and water. The phases were separated, and the aqueous phase extracted with 3 portions of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash chromatography (EtOAc/hexane, 2/8, v/v) to give the product.

Compound **4b**: yield 78%; d.e. >95%; IR (ν_{max}/cm^{-1}): 3501, 3055, 2953, 2869, 1732, 1678, 1388, 1259, 1388, 1259, 1174, 1064, 978, 908; ^{1}H NMR: δ 0.8–0.93 (m, 1H), 0.83 (d, J=6.4, 3H, CH$_3'$), 1.1–1.24 (m, 1H), 1.15 (s, 3H, CH$_3'$), 1.29 (s, 3H, CH$_3'$), 1.58–2.14 (m, 8H), 2.24–2.44 (m, 4H), 3.18 (d, J=6.4, 1H, OH), 3.74 (d, J=6.8, 1H, H7), 4.81–4.94 (td, J_1=4.4, J_2=10.8, 1H, H1′), 6.52 (t, J=4, 1H, H2), 7.12–7.28 (m, 5H, Ph); ^{13}C NMR: δ 21.8, 22.5, 22.9, 25.7, 26.2, 29.6, 31.2, 34.5, 37.9, 39.4, 40.9, 50.1, 70.6, 75.7 (C7), 125.0, 125.3, 127.9, 137.1 (C1), 150.0, 152.1 (C2), 172.0 (C6), 197.8 (C8); $[\alpha]_D$=+47.3 (*c* 0.78, $CHCl_3$). Elemental analysis found: C, 74.91; H, 8.36. $C_{24}H_{32}O_4$ requires: C, 74.97; H, 8.39%.

Compound **4c**: yield 76%; d.e. >95%; IR (ν_{max}/cm^{-1}): 3483, 2956, 2923, 2870, 1734, 1709, 1634, 1600, 1496, 1442, 1350, 1254, 1211, 1093, 1052, 978, 766, 702; ^{1}H NMR: δ 0.87 (d, J=6.2, 3H, CH$_3'$), 0.8–0.94 (m, 1H), 1.78 (s, 3H, CH$_3'$), 1.1–1.22 (m, 1H), 1.3 (s, 3H, CH$_3'$), 1.36–1.6 (m, 1H), 1.61–1.75 (m, 2H), 1.75–1.92 (m, 2H), 1.95–2.15 (m, 1H), 2.28–2.42 (m, 2H, H3), 2.50–2.62 (m, 2H, H4), 3.20 (d, J=5.8, 1H, OH), 3.87 (d, J=5.4, 1H, H6), 4.89 (td, J_1=4.4, J_2=10.8, 1H, H1′), 7.11–7.24 (m, 1H, H2), 7.23–7.33 (m, 5H, Ph); ^{13}C NMR: δ 21.8, 23.1, 26.2, 26.8, 29.5, 31.2, 34.4, 34.6, 39.4, 40.9, 50.1, 65.5, 76.2 (C6), 125.1, 125.3, 125.5, 128.0, 128.01, 142.7 (C1), 151.9, 161.6 (C2), 171.5 (C5), 207.0 (C7). $[\alpha]_D$=+30.0 (*c* 0.96, $CHCl_3$). Elemental analysis: found: C, 74.26; H, 8.23. $C_{23}H_{30}O_4$ requires: C, 74.56; H, 8.39%.

Compounds **4a**+**5a** (after acetylation): yield 45%; d.e. 8.7%; IR (ν_{max}/cm^{-1}): 3464, 2956, 2926, 2873, 1744, 1678, 1457, 1428, 1372, 1299, 1231, 1199, 1053, 964, 912, 888, 750; ^{1}H NMR: δ 0.69 (d, J=7, 3H, CH$_3{}^{a'}$), 0.78 (d, J=7, 3H, CH$_3{}^{b'}$), 0.845 (d, J=7, 3H, CH$_3{}^{a'}$), 0.895 (d, J=7, 3H, CH$_3{}^{b'}$), 0.82–0.94 (m, 2H), 0.97–1.10 (m, 3H), 1.33–1.41 (m, 2H), 1.42–1.52 (m, 2H), 1.62–1.71 (m, 5H), 1.89–1.97 (m, 2H), 1.97–2.10 (m, 5H), 2.12 (d, 3H, Ac^a), 2.13 (d, 3H, Ac^b), 2.36–2.55 (m, 9H), 4.63–4.69 (dt, J_1=4.5, J_2=11.5, 1H, H1$^{a'}$), 4.70–4.76 (dt, J_1=4.0, J_2=10.5, 1H, H1$^{b'}$), 5.90 (s, 1H, H7^a), 5.92 (s, 1H, H7^b), 7.11 (t, J=4.5, 1H, H2^a), 7.14 (t, J=4.5, 1H, H2^b); $[\alpha]_D$=–45.3 (*c* 1.0, $CHCl_3$). Elemental analysis found: C, 68.17; H, 8.88. $C_{20}H_{30}O_5$ requires: C, 68.54; H, 8.63%.

4.3. Crystallographic data

All measurements of crystal were performed on a Kuma KM4CCD κ-axis diffractometer with graphite-monochromated Mo Kα radiation. The crystal was positioned at 65 mm from the KM4CCD camera. 796 frames were measured at 1.6° intervals with a counting time of 12 sec. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wroclaw) programs.

The structure was solved by direct methods[22] and refined using SHELXL.[23] The refinement was based on F^2 for all reflections except those with very negative F^2 weighted R factors wR and all goodness-of-fit S values are based on F^2. Conventional R factors are based on F with F set to zero for negative F^2. The $F_o^2>2\sigma(F_o^2)$ criterion was used only for calculating R factors and is not relevant to the choice of reflections for the refinement. The R factors based on F^2 are about twice as large as those based on F. All hydrogen atoms were located from a differential map and refined isotropically. Scattering factors were taken from Tables 6.1.1.4 and 4.2.4.2 in Ref. 24.

Crystallographic data (excluding structural factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Center and allocated the deposition number CCDC 163739. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EW, UK (Fax: Int. code +(1223)-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Crystal data for $C_{24}H_{32}O_4$, **4b**: M=384.50, monoclinic, $P2(1)$, a=6.1167(12), b=9.7200(19), c=18.701(4) Å, V=1108.1(4) Å^3, Z=2, D=1.152 Mg m^3, T=293(2) K, 14374 measured reflections in the θ range for data collection 3.60–22.49°, R_{int}=0.0574, R_1=0.0433 for $I_o>2\sigma(I_o)$ and 0.0590 for all data.

Acknowledgements

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References

1. For an excellent review on Morita–Baylis–Hillman reaction, see: Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1997; Vol. 51, pp. 201–350.
2. Kataoka, T.; Iwama, T.; Tsuiyama, S.-i.; Iwamura, T.; Watanabe, S.-i. *Tetrahedron* **1998**, *54*, 11813–11824.
3. Drewes, S. E.; Emslie, N. D.; Khan, A. A. *Synth. Commun.* **1993**, *23*, 1215–1228.
4. Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317–4318.
5. Drewes, S. E.; Khan, A. A.; Rowland, K. *Synth. Commun.* **1993**, *23*, 183–188.
6. Barret, A. G. M.; Cook, A. S.; Kamimura, A. *Chem. Commun.* **1998**, 2533–2534.
7. Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220.
8. Bauer, T. *Tetrahedron: Asymmetry* **1996**, *7*, 981–984.
9. Bauer, T.; Jezewski, A.; Chapuis, C.; Kozak, J.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1391–1404.
10. Bauer, T.; Szymanski, S.; Jezewski, A.; Gluzinski, P.; Jurczak, J. *Tetrahedron: Asymmetry* **1997**, *8*, 2619–2625.
11. Bauer, T. *Tetrahedron* **1997**, *53*, 4663–4668.
12. Czapla, A.; Chajewski, A.; Kiegiel, K.; Bauer, T.; Wielogórski, Z.; Urbanczyk-Lipkowska, Z.; Jurczak, J. *Tetrahedron: Asymmetry* **1999**, *10*, 2101–2111.
13. Fikentscher, R.; Hahn, E.; Kud, A.; Oftring, A. *Ger. Offen.* DE 3,444,098, 1986; *Chem. Abstr.* **1986**, *107*, 7781s; *US Patent* 4,654,432, 1987.
14. Brown, J. M.; Rose, M.; Knight, F. I.; Wienand, A. *Rec. Trav. Chim. Pays-Bas* **1995**, *114*, 242–252.
15. Basawaiah, D.; Gowriswari, V. V. L. *Synth. Commun.* **1989**, *19*, 2461–2466.
16. Basawaiah, D.; Bharathi, T. K.; Gowriswari, V. V. L. *Tetrahedron Lett.* **1987**, *28*, 4351–4352.
17. Golubev, A. S.; Galakhov, M. V.; Kolomiets, A. F.; Fokin, A. V. *Izv. Nauk, Ser. Khim.* **1992**, 2763–2767; Engl. Transl. **1992**, 2193–2196.
18. Basavaiah, D.; Muthukumaran, K.; Sreenivasulu, B. *Synlett* **1999**, 1249–1250.
19. Whitesell, J. K.; Bhattacharaya, A.; Buchanan, C. M.; Chen, H. H.; Deyo, D.; James, D.; Liu, C.-L.; Minton, M. A. *Tetrahedron* **1986**, *42*, 2993–3001.
20. Bauer, T.; Jezewski, A.; Chapuis, C.; Jurczak, J. *Tetrahedron: Asymmetry* **1996**, *7*, 1385–1390.
21. Jurczak, J.; Zamojski, A. *Roczniki Chem.* **1968**, *42*, 255.
22. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.
23. Sheldrick, G. M. SHELXL-93. *Program for the Refinement of Crystal Structures*, University of Göttingen, Germany.
24. *International Tables for Crystallography*; Wilson, A. J. C., Ed.; Kluwer: Dordrecht, 1992; Vol. C.