Diastereoselective Access to the Spirotetronate Subunit of the Quartromicins

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Abstract: The *agalacto*-spirotetronate **B** subunit of quartromicins was synthesized in a predictible manner, following the Claisen–Ireland/metathesis approach (CIM strategy). Ene–yne ring-closure and selective mismatch Sharpless dihydroxylation are discussed as key steps, allowing an efficient approach to these structures.

Key words: quartromicin, ene–yne metathesis, Claisen–Ireland rearrangement, asymmetric dihydroxylation, spirotetronate

In 1991, an impressively complex family of compounds, the quartromicins, was isolated.[1] They exhibit a large spectrum of antiviral activity against herpes simplex virus type I, influenza virus type A and human immunodeficiency virus.[2] The highly symmetrical structure results from a junction between diastereoisomeric spirotetronate subunits A and B (Figure 1).

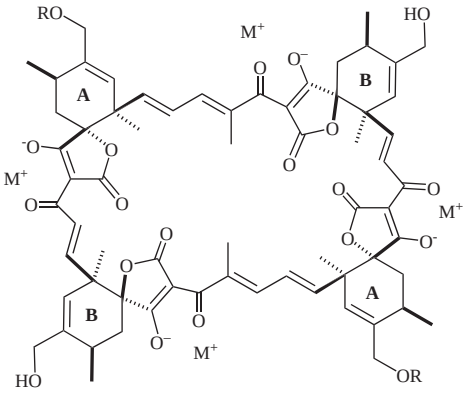

Figure 1 Quartromicin A_3 (R = α-D-galactosyl) and Quartromicin D_3 (R = H); $M^+ = Na^+, K^+, Ca^{2+}$.

Several natural products containing a quite similar central subunit have been isolated, such as chlorothricolide,[3] kijanolide,[4] okilactomycin,[5] tetronothiodin,[6] tetronolide,[7] ircinianin,[8] pyrrolosporin A,[9] PA-46101 A, A88696 C and F.[10]

Despite the exceptional work accomplished by Roush and co-workers in establishing the relative configurations of quartromicins,[11] to the best of our knowledge, no total synthesis has yet been published.

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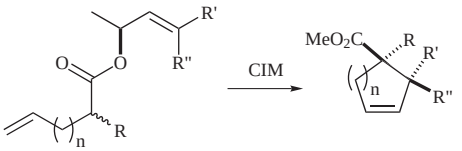
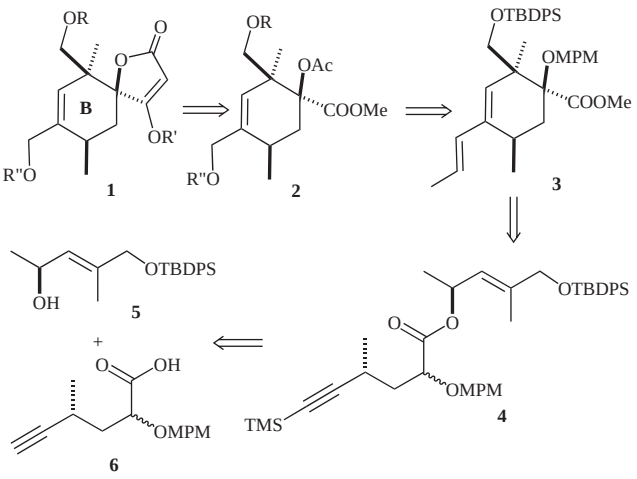
We have recently described a highly enantioselective sequential Claisen–Ireland/metathesis process (CIM) which allows the synthesis of cycloalkenes bearing two contiguous highly functionalized asymmetric centers (Scheme 1).[12]



Scheme 1 CIM: 1) KHMDS, PhMe, –78 °C; 2) TMSCl, –78 °C to r.t.; 3) Grubbs' I or II, CH_2Cl_2; 4) CH_2N_2, Et_2O.

In this article we would like to present our work concerning an approach to the type B backbone, using the following retrosynthetic analysis (Scheme 2). The target molecule **1** can be obtained through a Dieckmann reaction of compound **2**, with an in situ protection of the enolate. Ester **2** is derived from diene **3**, using a selective dihydroxylation and protecting group exchange. The key step of our approach is a Claisen–Ireland rearrangement followed by an ene–yne metathesis ring-closure to give **3** from the acyclic ester **4**. Compound **4** is easily obtained from allylic alcohol **5** and carboxylic acid **6**.

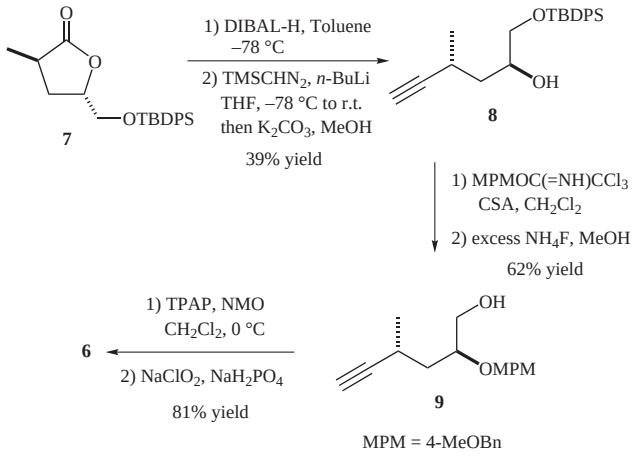


Scheme 2

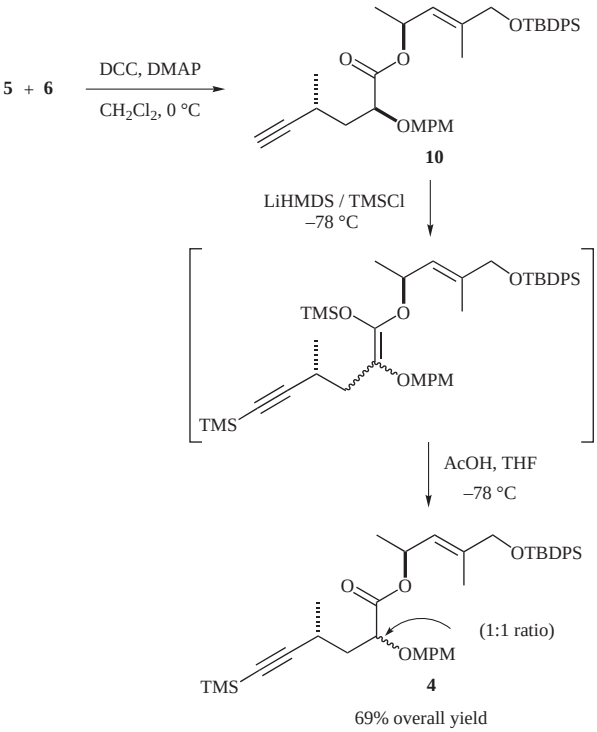
Synthesis of the Ester 4

Having previously prepared allylic alcohol **5**,[12] we turned our efforts to the synthesis of the chiral alkyne **6**. This compound can be made from the known enantiomerically

pure lactone **7**[13] in six steps after DIBAL-H reduction. Treatment of the resulting lactol with trimethylsilyl diazomethane enolate[14] gives the open chain alkyne. Overnight reaction in a mild basic methanolic media was required to isolate **8** in 39% overall yield.[15] Hydroxyl MPM protection under acidic conditions, followed by smooth ammonium fluoride deprotection gave the desired primary alcohol **9** in 62% yield. The absolute configuration of the MPM protected alcohol is not important at this stage, as it is lost in the Claisen–Ireland deprotonation step. Oxidation of the primary hydroxyl group in two steps with TPAP, NMO and sodium chlorite under buffered conditions then afforded the carboxylic acid **6** in 81% yield (Scheme 3).



Scheme 3

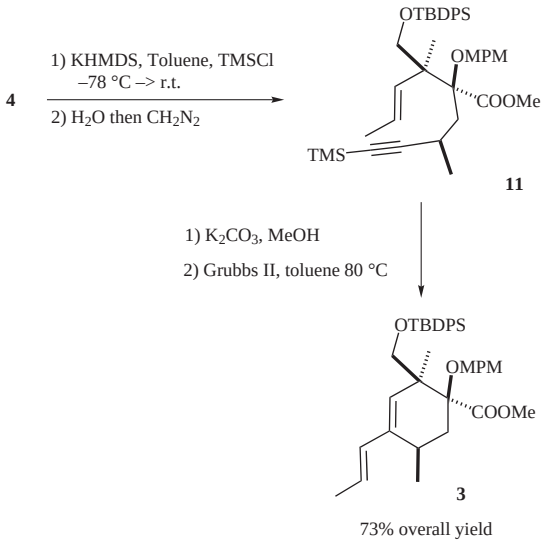


Scheme 4

Esterification of **5** and **6** under classical conditions (DCC, DMAP) and subsequent alkyne protection furnished the conveniently functionalized ester **4** (Scheme 4).[16]

Claisen–Ireland/Metathesis Sequence

The ester **4** was then submitted to the CIM process, using as a last step, a Grubbs II ene–yne metathesis (Scheme 5).[17,18]



Scheme 5

As we have previously observed in our model study, when the acetylenic moiety is unprotected, the diastereoselectivity in the Claisen–Ireland rearrangement drops. This particular behavior was tentatively explained by the generation of a double-metallated species at the beginning of the Claisen–Ireland process.[12]

The transition state involved in the CIM process is shown in Figure 2.

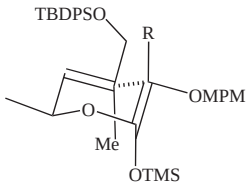
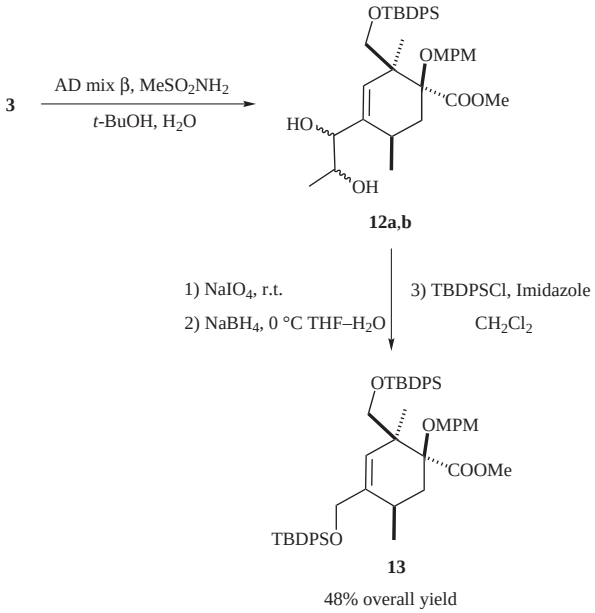


Figure 2

Access to the Spirotetronate Subunit

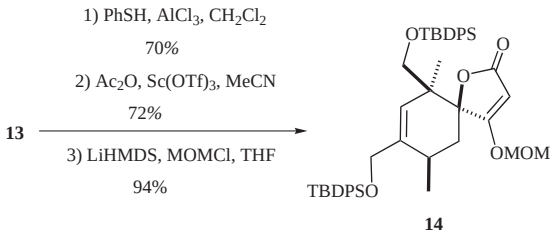
In order to selectively oxidize the external double bond of the cyclic derivative **3**, we anticipated that a mismatch Sharpless dihydroxylation with AD-mix reagent should cleanly and selectively touch this alkene. This remarkable transformation has already been observed[19] and we have applied it in a similar strategy during our total synthesis of (–)fumagillol.[20] The best result was obtained when **3** was treated with AD-mix β giving the diastereoisomeric mixture of **12a** and **12b**. Cleavage of the resulting 1,2-diol

with sodium periodate, direct sodium borohydride reduction, and protection of the primary alcohol resulted in the formation of the compound **13** in a 48% overall yield (Scheme 6).



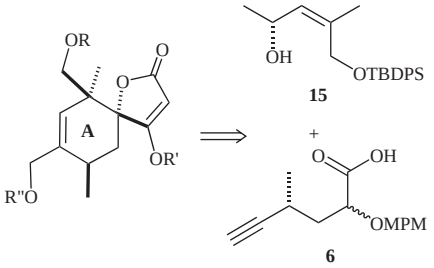
Scheme 6

Previous experience gained in the course of our fumagillol synthesis[20] showed that the deprotection of the MPM group with this kind of structure under known conditions (DDQ or CAN) can be problematic. The use of a strong nucleophile with a Lewis acid activation has been found to be a convenient solution. However, $BF_3{\cdot}OEt_2$/PhSH resulted in extensive deprotection of the TBDPS protecting groups and we preferred a smoother method using $AlCl_3$/PhSH.[21] The desired tertiary alcohol was obtained in 70% yield. Finally, acetylation followed by Dieckmann cyclization using conditions already applied by Roush and co-workers gave the quartromicins spirotetronate subunit B **14** (Scheme 7).[11a,c,d,22,23]



Scheme 7

In conclusion, we have shown that the CIM strategy can be efficiently applied to the synthesis of the spirotetronate subunit B of quartromicins. The subunit **A** is also accessible through the same CIM process by simply using the modified alcohol **15**,[24] previously prepared in our laboratory (Scheme 8). The transition state in the Claisen–Ireland rearrangement is depicted in Figure 3.



Scheme 8

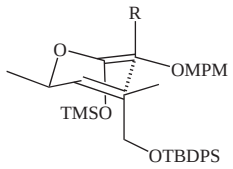


Figure 3

We are currently studying this new approach, as well as the total synthesis of quatromicins and analogous compounds.

Acknowledgment

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References

(1) (a) Kusumi, T.; Ichikawa, A.; Kakisawa, H.; Tsunakawa, M.; Konishi, M.; Oki, T. *J. Am. Chem. Soc.* **1991**, *113*, 8947. (b) Yoshii, E.; Takeda, K. *Recent Prog. Chem. Synth. Antibiot. Relat. Microb. Prod.* **1993**, 67.

(2) (a) Tsunakawa, M.; Tenmyo, O.; Tomita, K.; Naruse, N.; Kotake, C.; Miyaki, T.; Konishi, M.; Oki, T. *J. Antibiotics* **1992**, *45*, 180. (b) Tanabe-Tochikura, A.; Nakashima, H.; Murakami, T.; Tenmyo, O.; Oki, T.; Yamamoto, N. *Antiviral Chem. Chemother.* **1992**, *3*, 345.

(3) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411.

(4) (a) Mallams, A. K.; Puar, M. S.; Rossman, R. R.; Mc Phail, A. T.; Macfarlane, R. D.; Stephens, R. L. *J. Org. Chem.* **1992**, *57*, 2987. (b) Marshall, J. A.; Xie, S. *J. Chem. Soc, Perkin Trans. 1* **1983**, 1497.

(5) Imai, H.; Kaniwa, H.; Tokunaga, T.; Fujita, S.; Furuya, T.; Matsumoto, H.; Shimizu, M. *J. Antibiot.* **1987**, *40*, 1483.

(6) Ohtsuka, T.; Nakayama, N.; Itezono, Y.; Shimma, N.; Kuwahara, T.; Yokose, K.; Seto, H. *J. Antibiot.* **1993**, *46*, 18.

(7) Hirayama, N.; Kasai, M.; Shirahata, K.; Ohashi, Y.; Sasada, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2984.

(8) Takeda, K.; Sato, M.; Yoshii, E. *Tetrahedron Lett.* **1986**, *33*, 3903.

(9) Schroeder, D. R.; Colson, K. L.; Klohr, S. E.; Lee, M. S.; Matson, J. A.; Brinen, L. S.; Clardy, J. *J. Antibiot.* **1996**, *49*, 865.

(10) Bonjouklian, R.; Mynderse, J. S.; Hunt, A. H.; Deeter, J. B. *Tetrahedron Lett.* **1993**, *34*, 7857.

(11) (a) Roush, W. R.; Barda, D. A. *Tetrahedron Lett.* **1997**, *51*, 8781. (b) Roush, W. R.; Barda, D. A. *Org. Lett.* **2002**, *9*, 1539. (c) Roush, W. R.; Limberakis, C.; Barda, D. A. *Org. Lett.* **2002**, *9*, 1543. (d) Roush, W. R.; Barda, D. A.; Limberakis, C.; Kunz, R. K. *Tetrahedron* **2002**, *58*, 6433.

(12) Français, A.; Bedel, O.; Picoul, W.; Meddour, A.; Courtieu, J.; Haudrechy, A. *Tetrahedron*: *Asymmetry* **2005**, *16*, 1141.
(13) (a) $[\alpha]_D^{20}$ +37.5 (*c* 0.6, $CHCl_3$) very close to the literature {$[\alpha]_D^{20}$ +37.7 (*c* 0.4, $CHCl_3$)}. (b) Hanessian, S.; Murray, P. J.; Sahoo, S. P. *Tetrahedron Lett.* **1985**, *26*, 5623. (c) Herdeis, C.; Lütsch, K. *Tetrahedron: Asymmetry* **1993**, *1*, 121.
(14) Myers, A. G.; Goldberg, S. D. *Angew. Chem. Int. Ed.* **2000**, *39*, 2732.
(15) Ohira, S.; Okai, K.; Moritani, T. *J. Chem. Soc., Chem. Commun.* **1992**, 721.
(16) (a) O'Neil, S. V.; Quickley, C. A.; Snider, B. B. *J. Org. Chem.* **1997**, *62*, 1970. (b) Rancourt, J.; Burke, S. D. *J. Am. Chem. Soc.* **1991**, *113*, 2335.
(17) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
(18) **Typical CIM Procedure.**
Ester **4** (900 mg, 1.34 mmol) was dissolved in dry toluene (17 mL) under argon and then cooled to –78 °C. A solution of KHMDS in toluene (0.5 M) was added dropwise (4 mL, 2 mmol, 1.5 equiv) during 15 min. After 45 min, freshly distilled TMSCl (540 μL) was added and the resulting mixture was stirred for 5 min. Then, the mixture was warmed to r.t. and stirred for additional 3 h. The mixture was hydrolyzed with a 10% NH_4Cl (aq) solution and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 20 mL), and the combined organic layers were dried, filtered, and the solvent was removed under reduced pressure. The crude product was esterified with diazomethane, and after evaporation dissolved in MeOH (15 mL). Excess of solid K_2CO_3 (5.4 mmol, 630 mg, 4 equiv) was added in one portion and this suspension was stirred overnight at r.t. After evaporation under reduced pressure, the product was dissolved in Et_2O (30 mL) and washed with H_2O (15 mL). The layers were separated and the aqueous one was extracted with Et_2O (2 × 25 mL). The combined organic layers were dried, filtered and concentrated.
The compound was dissolved in toluene (40 mL) under an argon atmosphere, and a solution of second generation Grubbs' catalyst (90 mg, 0.105 mmol, 0.08 equiv) in toluene (5 mL) was then added. This solution was heated to 80 °C for 1 h. After cooling down, the mixture was concentrated, and the crude product was purified by silica gel column chromatography (175 g SiO_2, Et_2O–*n*-pentane, 1:5) to afford pure cyclized methyl ester **3** (747 mg, 73% yield for four steps).
Data for compound **3**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.66 (4 H, m, C_{Ar}–H), 7.38 (6 H, m, C_{Ar}–H), 7.05 (2 H, d, C_{MPMar}–H, *J* = 8.5 Hz), 6.74 (2 H, d, C_{MPMar}–H, *J* = 8.5 Hz), 5.90–6.05 (1 H, m, C_4–*CH*CHMe), 5.74 (1 H, s, C_3–H), 5.55–5.70 (1 H, m, C_4–CH*CH*Me), 4.02–4.46 (2 H, AB syst., Ar–*CH*$_2$), 3.95–4.10 (2 H, m, C_2–C*H*$_2$–OSi), 3.78 (3 H, s, OMe), 3.57 (3 H, s, COOMe), 2.71 (1 H, m, C_5–H), 2.25–2.35 (1 H, m, C_6–Ha), 2.00–2.09 (1 H, m, C_6–Hb), 1.78 (3 H, d, C_4–CHCH*Me*, *J* = 6.25 Hz), 1.16 (3 H, d, C_5–*Me*, *J* = 7.25 Hz), 1.11 (9 H, s, *t*-Bu), 1.03 (3 H, s, C_2–*Me*) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 173.4 (*C*OOMe), 158.6 (C_{qAr}–OMe), 136.7 (C_4), 135.7 (C_{Ar}), 134.0 (C_{MPMar}–CH_2O), 133.8 (C_{qAr}), 132.7 (C_3), 130.5 (C_4–*C*HCHMe), 129.3 (C_{Ar}), 128.0 (C_{Ar}), 127.4 (C_{Ar}), 123.2 (C_4–CH*C*HMe), 113.5 (C_{Ar}), 84.3 (C_1), 67.6 (C_{MPMar}–*C*H$_2$O), 65.8 (C_2–*C*H$_2$–OSi), 55.2 (ArO*Me*), 51.3 (COO*Me*), 43.8 (C_2), 30.7 (C_5), 28.1 (C_6), 26.9 (Si*CMe*$_3$), 21.9 (C_2–*Me*), 20.4 (C_5–*Me*), 17.0 (Si*C*Me$_3$) ppm. $[\alpha]_D^{20}$ +17.3 (*c* 1.2, $CHCl_3$). HRMS (ES): *m/z* calcd [M + Na]: 635.3169; found: 635.3183.
(19) (a) Sedrani, R.; Thai, B.; France, J.; Cottens, S. *J. Org. Chem.* **1998**, *63*, 10069. (b) Andrus, M. B.; Lepore, S. D.; Sclafani, J. A. *Tetrahedron Lett.* **1997**, *38*, 4043. (c) Matsuo, G.; Miki, Y.; Nakata, M.; Matsumura, S.; Toshima, K. *J. Org. Chem.* **1999**, *64*, 7101. (d) Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7047.
(20) Bedel, O.; Haudrechy, A.; Langlois, Y. *Eur. J. Org. Chem.* **2004**, 3813.
(21) Bouzide, A.; Sauvé, G. *Synlett* **1997**, 1153.
(22) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413.
(23) Data for compound **14**: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.66 (4 H, m, C_{Ar}–H), 7.35 (6 H, m, C_{Ar}–H), 5.44 (1 H, br d, C_3–H), 5.16 (1 H, s, CO–CH), 5.01 (2 H, 2 collapsed d, O–CH_2–O), 4.25 (1 H, d, C_4–C*H*$_2$–OSi, *J* = 12.8 Hz), 4.08 (1 H, d, C_4–C*H*$_2$–OSi), 3.73 (1 H, d, C_2–C*H*$_2$–OSi, *J* = 9.5 Hz), 3.63 (1 H, d, C_2–C*H*$_2$–OSi, *J* = 9.5 Hz), 3.37 (3 H, s, OMe), 2.77 (1 H, m, C_5–H), 2.13 (1 H, dd, C_6–Ha, *J* = 9.8 Hz, *J* = 13.7 Hz), 1.89 (1 H, dd, C_6–Ha, *J* = 7 Hz, *J* = 13.7 Hz), 1.05 (24 H, m, C_5–*Me*, C_2–*Me*, 2 *t*-Bu) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 182.7 (*C*O–CH_2–O), 172.2 (*C*O), 139.9 (C_4), 135.9 (C_{Ar}), 135.8 (C_{Ar}), 135.6 (C_{Ar}), 134.0 (C_{Ar}), 133.8 (C_{Ar}), 133.4 (C_{Ar}), 129.9 (C_{Ar}), 129.8 (C_{Ar}), 129.7 (C_{Ar}), 127.8 (C_{Ar}), 127.7 (C_{Ar}), 126.8 (C_3), 96.9 (O*Me*), 91.2 (CO–*C*H), 87.4 (O–*C*H$_2$–O), 70.2 (C_4–*C*H$_2$–OSi),, 66.0 (C_2–*C*H$_2$–OSi), 57.5 (C_1), 42.5 (C_2), 38.2 (C_5), 29.8 (C_6) 29.2 (C_5–*Me*), 27.0 (C_2–*Me*), 26.9 (2 Si*CMe*$_3$), 19.5 19.4 (Si*C*Me$_3$). $[\alpha]_D^{20}$ –3.2 (*c* 0.3, $CHCl_3$). HRMS (ES): *m/z* calcd [M + H]: 775.3850; found: 775.3875.
(24) Bedel, O. PhD Thesis, personal results.