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Novel protection of 1,2-diol for *trans*-dihydroxycyclopentene ring construction by the C—H insertion of alkylidene carbene: Formal total synthesis of (+)-trehazolin

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ABSTRACT

The chiral vicinal diol was protected as 6-methylene-1,4-dioxepane to construct a cyclopentene ring by the C—H insertion of alkylidene carbene. The removal of the protecting group was achieved in a few steps, affording the corresponding diol in a reasonable yield. Using these reactions, the known synthetic intermediate for (+)-trehazolin was synthesized from D-diethyl tartrate. In addition, a short route to the intermediate from a D-mannitol derivative was described.

The C—H insertion of alkylidene carbene, which is one of the direct C—H bond functionalization methods [1], is beneficial for the construction of a cyclopentene ring. Since the report of the generation of alkylidene carbenes using lithiotrimethylsilyldiazomethane and ketones by our group [2], this reaction has been used as a key reaction for natural product synthesis [2,3,4]. In a series of studies, an antitumor agent (−)-neplanocin A containing the *cis*-dihydroxycyclopentene ring was synthesized *via* cyclopentene **1** which was obtained by the C—H insertion of alkylidene carbene from ketone **2** (Fig. 1) [2i,5].

On the other hand, the reaction between lithiotrimethylsilyldiazomethane and chiral epoxide **3** afforded cyclopentene **4**, which served as the precursor for *trans*-dihydroxycyclopentene derivative **5**. In turn, **5** was transformed into a known intermediate **6** for the glycosidase inhibitor (+)-trehazolin (Fig. 2) [2c,6]. This strategy was selected to prevent the formation of a stable oxonium ylide, which occurred when the dihydroxyl group was protected as a non-cyclic bis ether. The formation of the oxonium ylide often prevented smooth C—H insertion, although the equilibrium between the carbene and the ylide was possible [2c,7].

In this study, the direct protection of a potential *trans*-vicinal diol as a cyclic ether was attempted. After unsuccessful results were obtained with known protecting groups for the *trans*-vicinal diol [8], it was found that reaction of 1,4-dioxepane derivative **7** and lithiotrimethylsilyldiazomethane afforded cyclopentene **8a** and its epimer **8b** in a combined yield of 69%. Cyclopentene **8a** could be converted into the synthetic intermediate **6**. As the stereoselective reduction of ketone **9** was possible, cyclopentene **8a** was synthesized in much shorter way from the D-mannitol derivative *via* ketone **10** and cyclopentene **11** (Fig. 2).

Ketone **7** was prepared from D-diethyl tartrate (**12**) (Scheme 1). The protection of the vicinal diol of **12** as an acetonide, followed by the reduction of esters by lithium borohydride [9] afforded diol **13**. The hydroxyl groups of **13** were protected as a bis *p*-methoxybenzyl (PMB) ether, and the acetonide was removed using acidic methanol to yield diol **14**. This reaction incompletely ended; hence, the starting material was recovered and re-used. Compound **14** was subjected to the reaction with sodium hydride and 3-chloro-2-chloromethyl-1-propene affording 2-methylene-1,3-propyl ether **15**. The partial deprotection of PMB ethers using one equivalent of DDQ afforded mono alcohol **16**. Alcohol **16** was transformed to diol **17** by the oxidation of **16**, reaction with ethoxyethoxymethyllithium [10] and acidic treatment of the product. The protection of the primary alcohol of **17** as TBS ether and IBX oxidation of the secondary alcohol afforded ketone **7**. The alkylidene carbene generated from **7** underwent C—H insertion, affording **8a** and **8b** in 36% and 33% yield, respectively [11]. The stereochemistry of **8a** and **8b** was determined by an NOE experiment [12].

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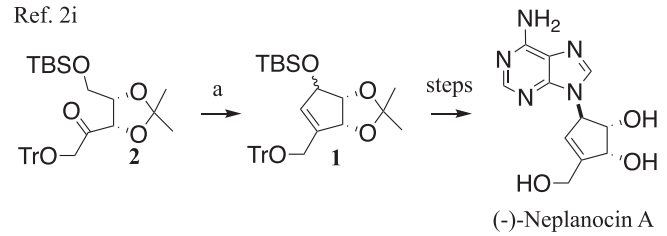


Fig. 1. Reagents and conditions: (a) $TMSCLiN_2$, THF, 55–65%.

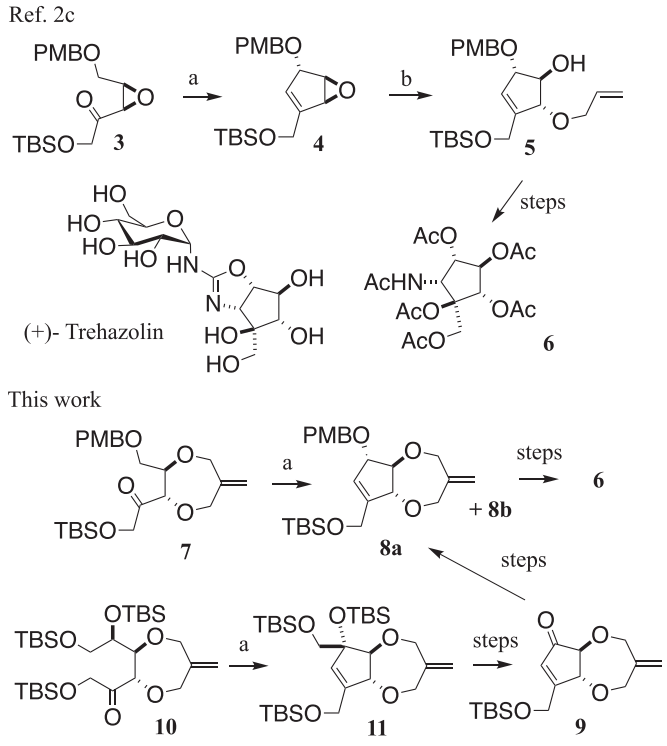
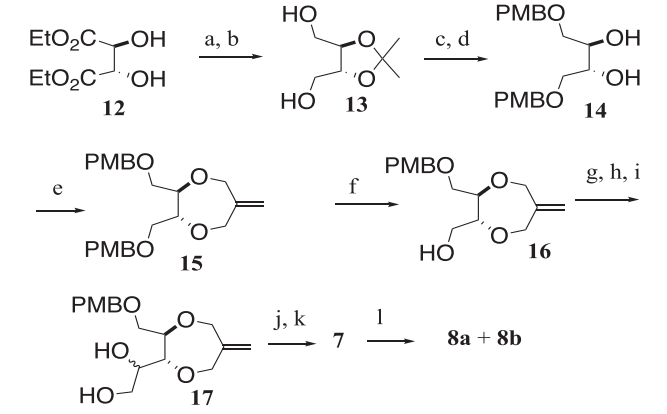


Fig. 2. Reagents and conditions: (a) $TMSCLiN_2$, THF or DME, 49%–69%; (b) allyl alcohol, *p*-TsOH, 69%.



Scheme 1. Reagents and conditions: (a) DMP, *p*-TsOH, CH_2Cl_2, 40 °C, 17 h, 90%; (b) $NaBH_4$, LiCl, THF–EtOH, rt, 14 h, 92%; (c) PMBCl, NaH, TBAI, DMF, rt, 3 h, 93%; (d) MeOH, *p*-TsOH, rt, 5 h, 46% (37% of SM); (e) 3-chloro-2-chloromethyl-1-propene, NaH, DMF, 60 °C, 3 h, 72%; (f) DDQ, CH_2Cl_2-H_2O, rt, 2 h, 40% (50% of SM); (g) IBX, DMSO, 50 °C, 1 h, 70%; (h) Bu_3SnCH_2OEE, BuLi, THF, −78 °C, 20 min, 75%; (i) MeOH, PPTS, 0 °C, 23 h, 76%; (j) TBSCl, imidazole, DMF, rt, 0.5 h, 88%; (k) IBX, DMSO, 50 °C, 2 h, 73%; (l) $TMSCHN_2$, BuLi, DME, −78 °C, 0.5 h to rt, 0.5 h, 36% of **8a**, 33% of **8b**.

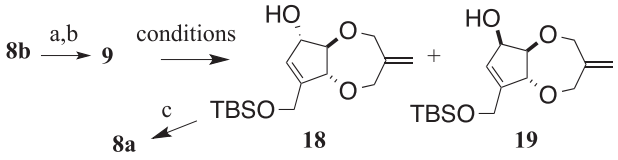
The undesired isomer **8b** was converted to ketone **9** and the stereoselective reduction was attempted (Scheme 2). Luche reduction selectively gave the desired alcohol **18**, which was converted to **8a**. It is noteworthy that lithium tri-*sec*-butylborohydride showed reversed high stereoselectivity giving the other isomer **19**.

The generation of the diol from 6-methylene-1,4-dioxepane was investigated using **20** and **21** (Scheme 3). Various conditions for the deprotection of allyl ether were not effective for these compounds; however, $RuHCl(CO)(PPh_3)_3$ [13] cleanly catalyzed the isomerization of double bond of **20** to **22**. The acidic hydrolysis of **22**, followed by β-elimination from the resulting aldehyde afforded diol **23**. Using acid-sensitive substrate **21**, diol **24** was cleanly obtained by hydroboration-oxidation and IBX oxidation, followed by the treatment of the resulting aldehyde **25** with potassium carbonate in methanol (β-elimination, Michael addition of methanol to the α, β-unsaturated aldehyde, and β-elimination of the substrate).

With the deprotection procedure to the diol in hand, the formal synthesis of (+)-trehazolin from **8a** was focused (Scheme 4). The deprotection of the TBS ether of **8a**, Sharpless asymmetric epoxidation, and MOM protection of the alcohol afforded cyclopentane **26**. The generation of the *trans*-diol *via* aldehyde **27** and MOM protection afforded the known synthetic intermediate **28**, which was convertible to **6** [2c,14].

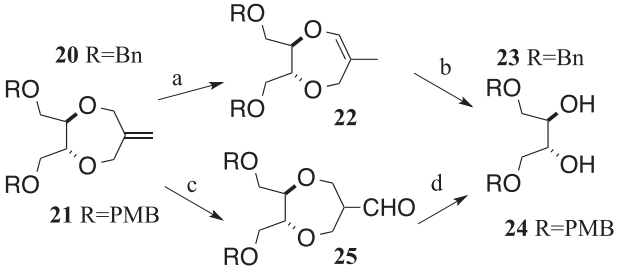
The overall yield to **16** was improved by using allylic bis(*tert*-butyl carbonate) **29** with a palladium catalyst in the first step [15]. After this mild reaction, diester **30** was converted to mono alcohol **16** in two steps (Scheme 5).

As the reduction of **9** was highly stereoselective, an alternative short approach to **9** starting from the commercially available D-mannitol derivative **31** was investigated (Scheme 6). After the protection of the diol, acetonides of **32** were removed, and three hydroxyl groups of the tetraol **33** were protected as tris-TBS ether **34**. By-products **35** and **36** were combined and treated with acidic ethanol, regenerating **33**. The IBX oxidation of secondary alcohol of

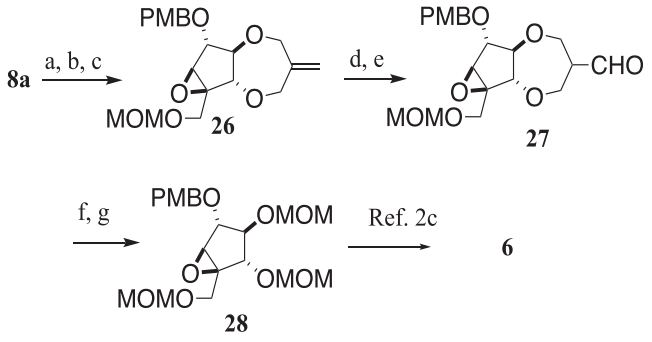


conditions	yield	18:19
DIBAL, CH_2Cl_2, -78°C	86%	4:1
$NaBH_4$, $CeCl_3$ MeOH, THF , rt	80%	20:1
Li (*sec*-Bu)$_3$H , THF, -78°C	96%	1:33

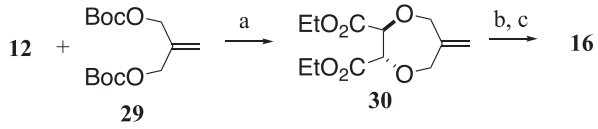
Scheme 2. Reagents and conditions: (a) DDQ, CH_2Cl_2-H_2O, rt, 2 h, 31%; (b) IBX, DMSO, 50 °C, 2 h, 26%; (c) PMBCl, NaH, TBAI, DMF, 0 °C, 2 h, 53%.



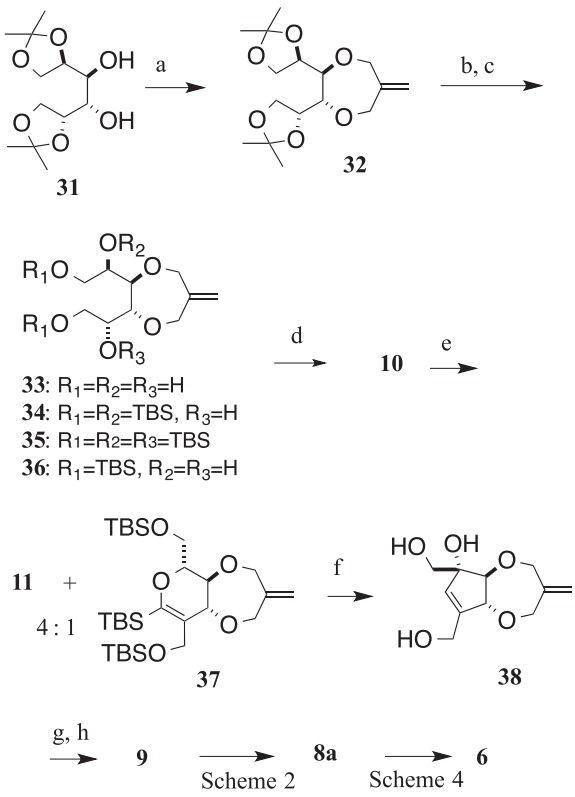
Scheme 3. Reagents and conditions: (a) $RuHCl(CO)(PPh_3)_3$, THF, reflux, 24 h, 94%; (b) AcOH-H_2O, 70 °C, 48 h, 75%; (c) BH_3·THF, rt, 1 h; 10% NaOH, 30% H_2O_2, rt, 1 h, 95%; IBX, DMSO, 50 °C, 1 h, 75%; (d) K_2CO_3, MeOH, 50 °C, 1 h, 94%.



Scheme 4. Reagents and conditions: (a) TBAF, THF, rt, 5 h, 92%; (b) L-diethyl tartrate, TBHP, $Ti(OiPr)_4$, CH_2Cl_2, 0 °C, 19 h, 57%; (c) MOMCl, NaI, $(iPr)_2NEt$, DME, rt, 1 h, 90%; (d) 9-BBN, THF, rt, 1 h; 6M NaOH, 30% H_2O_2, rt, 1 h, 56%; (e) IBX, CH_3CN, 70 °C, 1 h,; (f) MeOH, K_2CO_3, rt, 2.5 h, 83% in two steps; (g) MOMCl, $(iPr)_2NEt$, CH_2Cl_2, rt, 2 h, 83%



Scheme 5. Reagents and conditions: (a) $Pd_2(dba)_3$, dppb, THF, rt, 67 h, 75%; (b) LiCl, $NaBH_4$, THF–EtOH, rt, 19 h, 91%; (c) PMBCl, NaH, TBAI, DMF, rt, 3 h, 60%



Scheme 6. Reagents and conditions: (a) 3-chloro-2-chloromethyl-1-propene, NaH, DMF, 60 °C, 2 h, 60%; (b) EtOH–1M HCl (10:1), 80 °C, 2 h; (c) TBSCl, imidazole, DMF, rt, 1 h, 55% in two steps (>29% of **35** and **36**); (d) IBX, pyridine, DMSO, 50 °C, 1 h, 97%; (e) $TMSCHN_2$, BuLi, DME, −78 °C, 0.5 h, then rt, 0.5 h, 85% (combined); (f) KF, 18-crown-6-ether, DMF–H_2O (10:1), 80 °C, 14 h, 73%; (g) $Pb(OAc)_4$, THF, −20 °C, 1.5 h, 67%; (h) TBSCl, imidazole, DMF, rt, 2 h, 94%.

34 gave the ketone **10,** which was treated with lithiotrimethylsilyldiazomethane to afford a mixture of **11** and **37** in a ratio of 4:1. Compound **37** was obtained as the product from silyl-group transfer of the cyclic oxonium ylide [2c,5,7]. Both isomers were separated by preparative thin-layer chromatography and characterized [16]. Practically, a mixture of **11** and **37** was treated with potassium fluoride in the presence of 18-crown-6-ether [17] and silica-gel column chromatography of the products afforded pure triol **38**. Triol **38** was converted to ketone **9** by glycol fission using lead tetra acetate, followed by the protection of the alcohol. Ketone **9** was converted into **8a**, and then into **6** (Scheme 2, Scheme 4).

In conclusion, the vicinal diol protected as 6-methylene-1,4-dioxepane was used to construct the cyclopentene ring which contains *trans*-vicinal diol by the C—H insertion of alkylidene carbene. The removal of the 3-methylene-1,3-propyl group was possible in two ways. Since the number of cyclic protecting groups for *trans*-vicinal diol is limited [8], our findings may provide another choice of protecting group. Reversed high stereoselectivity in the reduction of carbonyl group adjacent to this protecting group is also notable. Using these novel transformations, new formal routes to (+)-trehazolin were established.

Acknowledgments

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[8] Unsatisfactory results were obtained with known protecting groups: 1,3-(1,1,3,3-Tetraisopropyldisiloxanylidene) derivatives were not stable for multistep transformations. The ketone derived from butane-2,3-diacetal-protected tartrate[18] did not afford the C–H insertion product with lithiotrimethlsilyldiazomethane. 1,3-O-(o-xylylene) protection with simple vicinal diols only proceeded with a non-practically low yield.
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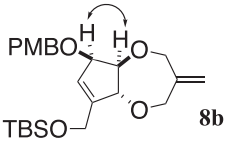
[11] **8a**: $[\alpha]_D^{24}$ −20° (*c* 0.59 ,$CHCl_3$); ν_{max}(neat)/cm^{-1} 1610, 1514, 1464; ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.9 (s, 9H), 3.0 (s, 3H), 3.96 (t, 1H, *J* = 6.1 Hz), 4.1 (d, 1H, *J* = 4.9 Hz), 4.21 (d, 1H, *J* = 5.4 Hz), 4.23 (q, 1H, *J* = 1.5 Hz), 4.27–4.29 (m, 1H), 4.31–4.35 (m, 1H), 4.42 (t, 1H, *J* = 12.5 Hz), 4.55 (d, 1H,

J = 11.7 Hz), 4.67 (d, 1H, *J* = 11.7 Hz), 5.25 (brd, 1H, *J* = 2.9 Hz), 5.65 (quint, 1H, *J* = 1.7 Hz), 6.7 (d, 2H, *J* = .5 Hz), 7.30 (2H, d, *J* = = .5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.40, −5.29, 1.40, 25.93, 55.29, 59.73, 71.40, 73.50, 73.57, 77.21, 1.52, 4.72, 94.21, 113.71, 120.9, 124.29, 129.31, 130.56, 143.54, 144.9, 159.04. **b**: $[\alpha]_D^{24}$ +51° (*c* 0.665 ,$CHCl_3$); ν_{max}(neat)/cm^{-1} 1613, 1514, 1463; ^{1}H NMR (400 MHz, $CDCl_3$) δ δ 0.05 (s, 3H), 0.06 (s, 3H), 0.90 (s, 9H), 3.77 (t, 1H, *J* = 6.0 Hz), 3.0 (s, 3H), 4.23 (d, 1H, *J* = 11.6 Hz), 4.25 (s, 2H), 4.26 (d, 1H, *J* = 12.0 Hz), 4.33 (brs, 1H), 4.41 (d, 1H, *J* = 12.0 Hz), 4.53 (d,1H, *J* = 11.6 Hz), 4.55 (d, 1H, *J* = = 12.0 Hz), 4.66 (d, 1H, *J* = 12.0 Hz), 4.99 (brd, 1H, *J* = 6.0 Hz), 6.6 (dd, 2H, *J* = 6.0 Hz, 1.6 Hz), 7.2 (dd, 2H, *J* = 6.0 Hz, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.35, −5.33, 1.39, 25.91, 55.25, 60.02, 70.90, 73.3, 73.54, 76.92, 5.35, 7.01, 113.5, 120.62, 122., 129.39, 130.7, 144.96, 149.27, 15.90.

[12] In the NOESY spectrum of **8b**, a strong cross peak was observed between the cis protons (δ3.77 and 4.33) of the cyclopentene ring.



8b

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[14] **28**: $[\alpha]_D^{26}$ +6.1° (*c* 0.89 , $CHCl_3$); ν_{max}(neat)/cm^{-1} 1613, 1586, 1514; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.35 (3H, s), 3.36 (3H, s), 3.43 (3H, s), 3.52 (1H, s), 3.61 (1H, d, *J* = 11.9 Hz), 3.81 (3H, s), 3.90 (1H, s), 4.14 (1H, s), 4.18 (1H, s), 4.24 (1H, d, *J* = 11.8 Hz), 4.53 (1H, d, *J* = 12.5 Hz), 4.56 (1H, d, *J* = 7.0 Hz), 4.64 (1H, d, *J* = 6.4 Hz), 4.65 (1H, d, *J* = 12.5 Hz), 4.67 (1H, d, *J* = 7.0 Hz), 4.78 (2H, s), 6.89, (2H, brd, *J* = 8.6 Hz), 7.29 (2H, brd, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.26, 55.33, 55.45, 55.73, 61.08, 63.58, 67.33, 71.54, 79.62, 81.54, 85.73, 95.25, 96.12, 96.42, 113.88, 129.50, 159.43.

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[16] **11**: $[\alpha]_D^{13}$ −13° (c 0.62, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1471, 1463; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.06 (s, 3H), 0.065 (s, 3H), 0.073 (s, 3H), 0.08 (s, 3H), 0.13 (s, 3H), 0.849 (s, 9H), 0.854 (s, 9H), 0.91 (s, 9H), 3.45 (d, 1H, *J* = 9.7 Hz), 3.66 (d, 1H, *J* = 9.7 Hz), 3.82 (1H, d, *J* = 5.8 Hz), 4.15 (t, 1H, *J* = 12.8 Hz), 4.16 (d, 1H, *J* = 12.8 Hz), 4.29 (d, 1H, *J* = 15.3 Hz), 4.32 (d, 1H, *J* = 5.8 Hz), 4.39 (d, 1H, *J* = 12.4 Hz), 4.44 (d, 1H, *J* = 12.4 Hz), 5.20 (s, 1H), 5.22 (s, 1H), 5.64 (t, 1H, *J* = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.55, −5.46, −5.43, −2.62, −2.58, 18.06, 18.24, 18.29, 25.74, 25.85, 25.92, 59.83, 65.85, 73.40, 73.49, 83.03, 84.23, 95.06, 120.22, 128.90, 142.99, 145.54. **37**: $[\alpha]_D^{14}$ +19° (*c* 0.67, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1653, 1617, 1507; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s 3H), 0.07 (s, 3H), 0.08 (s, 3H), 0.12 (s, 3H), 0.15 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 0.90 (s, 9H), 3.63 (dd, 1H, *J* = 10.4 Hz, 7.5 Hz), 3.68 (dq, 1H, *J* = 10.4 Hz, 1.7 Hz), 3.83 (dd, 1H, *J* = .0 Hz, 1.8 Hz), 3.86 (dd, 1H, *J* = .0 Hz, 3.7 Hz), 4.00 (d, 1H, *J* = 10.7 Hz), 4.19 (d, 1H, *J* = 7.4 Hz), 4.28 (t, 1H, *J* = 12.5Hz), 4.37 (d, 1H, *J* = .6 Hz), 4.44 (dd, 1H, *J* = 13.4 Hz, 3.2 Hz), 5.05 (s, 1H), 5.07 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.55, −5.50, −5.40, −5.29, −4.59, −4.32, 17., 18.22, 18.45, 25.81, 25.93, 26.68, 58.77, 61.83, 73., 73.13, 77.14, 77.69, 79.44, 4.16, 122.75, 147.69, 157.04.

[17] Use of TBAF for the deprotection afforded an inseparable mixture of products and reagents.

[18] S.V. Ley, D.K. Baeschlin, D.J. Dixon, A.C. Foster, S.J. Ince, H.W.M. Priepke, D.J. Reynolds, Chem. Rev. 101 (2001) 53–80.