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Conversion of D-Glucose to Cyclitol with Hydroxymethyl Substituent via Intramolecular Silyl Nitronate Cycloaddition Reaction: Application to Total Synthesis of (+)-Cyclophellitol

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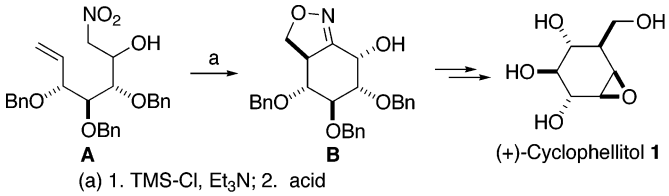
ABSTRACT



A diastereoisomeric mixture of 1-nitro-6-heptene-2,3,4,5-tetraol derivative (A) was prepared by Henry reaction between D-glucose-based aldehyde and nitromethane. Only the (2*S*)-isomer of A led to cyclitol (B) via nitronate-olefin cycloaddition on treatment with TMS-Cl and Et_3N in the presence of catalytic DMAP followed by acid treatment. (+)-Cyclophellitol (1) was synthesized from B in eight steps.

(+)-Cyclophellitol (**1**) was isolated from the culture of a mushroom *Phellinus* sp. by Umezawa and co-workers in 1990.[1] This molecule features a fully oxygenated cyclohexane ring plus a hydroxymethyl appendage and is known to have potent activity as an α-glucosidase inhibitor and also as a potential inhibitor of HIV.[2] In the same year, the first total synthesis of **1** was reported by Tatsuta.[3] Since then, the unique structural characteristic and the significant biological activities have attracted many organic chemists to develop effective methods for the synthesis of **1**.[4,5]

A sugar-based strategy should be highly attractive not only as total synthesis of the seven-carbon natural product of this class but also as a promising stereoselective carbocyclization accompanied by one-carbon introduction.[6] In this context, the enal (**3**) (Scheme 1) deserves consideration because of not only its ready availability from D-glucose in multigram quantities but also functional group assembly introducible through the Henry reaction with nitromethane. Such a process can provide the requisite one-carbon and, at the same time, a terminal nitro group that can serve as a reaction partner in a nitronate-olefin cycloaddition process leading to the desired

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(1) Atsumi, S.; Umezawa, K.; Iinuma, H.; Naganawa, H.; Nakamura, H.; Iitaka, Y.; Takeuchi, T. *J. Antibiot*. **1990**, *43*, 49−53.

(2) Atsumi, S.; Iinuma, H.; Nosaka, C.; Umezawa, K. *J. Antibiot*. **1990**, *43*, 1579−1585.

(3) For the first total synthesis of **1**, see: (a) Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Tetrahedron Lett*. **1990**, *31*, 1171−1172, (b) Tatsuta, K.; Niwata, Y.; Umezawa, K.; Toshima, K.; Nakata, M. *Carbohydr. Res*. **1991**, *222*, 189−203.

(4) For the enantioselective total synthesis of **1**, see: (a) Akiyama, T.; Ohnari, M.; Shima, H.; Ozaki, S. *Synlett* **1991**, 831−832. (b) Shing, T. K. M.; Tai, V. W.-F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2017−2025. (c) McDevitt, R. E.; Fraser-Reid, B. *J. Org. Chem*. **1994**, *59*, 3250−3252. (d) Sato, K.; Bokura, M.; Moriyama, H.; Igarashi, T. *Chem. Lett*. **1994**, 37−40. (e) Jung, M. E.; Choe, S. W. T. *J. Org. Chem*. **1995**, *60*, 3280−3281. (f) Schlessinger, R. H.; Bergstrom, C. P. *J. Org. Chem*. **1995**, *60*, 16−17. (g) Letellier, P.; Ralainairina, R.; Beaupère, D.; Uzan, R. *Synthesis* **1997**, 925−930. (h) Takahashi, H.; Iimori, T.; Ikegami, S. *Tetahedron Lett*. **1998**, *39*, 6939−6942. (i) Ziegler, F. E.; Wang, Y. *J. Org. Chem*. **1998**, *63*, 426−427; see also *J. Org. Chem*. **1998**, *63*, 7920−7930. (j) Trost, B. M.; Patterson, D. E.; Hembre, E. J. *Chem. Eur. J*. **2001**, *7*, 3768−3775.

(5) For a review, see: Marco-Contelles, J. *Eur. J. Org. Chem*. **2001**, 1607−1618.

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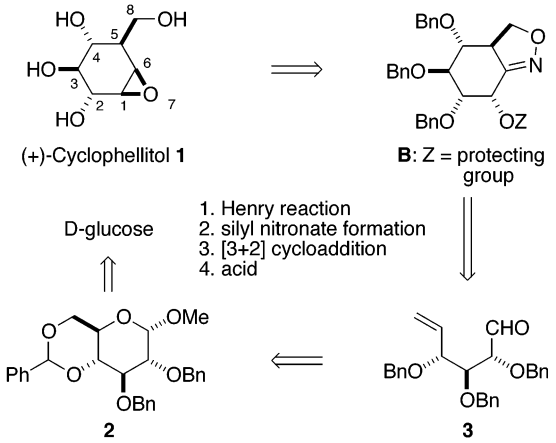
Scheme 1



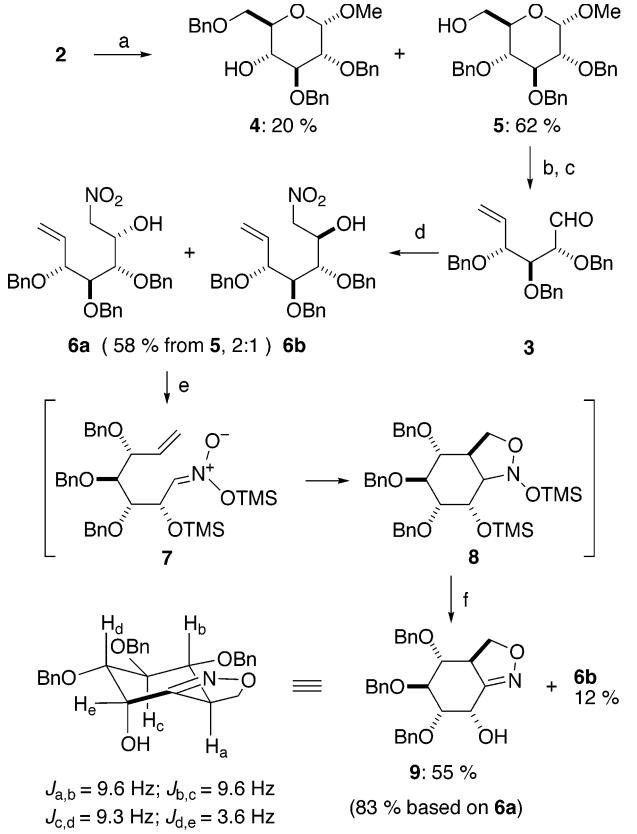
cyclohexane ring formation. Furthermore, a cycloadduct to be furnished through this process will bear reasonable functionalities required for the elaboration of the remaining oxygen-centered structures of **1**.

Such a plan is outlined in Scheme 1 in which the benzylidene acetal (**2**), available readily from D-glucose, is chosen as a starting material that can be transformed to the desired enal **3**. The Henry reaction between **3** and nitromethane followed by chlorotrimethylsilane treatment may lead to intramolecular silyl nitronate cycloaddition reaction[7] to result in the formation of the desired cycloadduct (**B**) after acidic treatment as indicated in Scheme 1. Stereochemical outcome of this process might be reasonably estimated on the basis of a transition state structure model that is bicyclic and concerted in nature and expected to be an acceptable level of stereoselectivity. If this is the case, we can establish a highly concise and effective strategy for converting sugar-based ω-enals to six-membered carbocycles bearing both a hydroxymethyl group and a functional group equivalent to a carbonyl group on the ring. In this communication we describe the realization of this goal and also enantioselective total synthesis of **1** using thus-obtained functionalized cyclitol derivative **B**.

Regioselective reductive cleavage of known benzylidene acetal[8] (**2**), prepared from methyl α-D-glucopyranoside by means of borane/BF_3·OEt_2 combination,[9] gave a separable mixture of desired alcohol (**5**) and the minor isomer (**4**) in a 3:1 ratio. Bromination of **5** followed by zinc-mediated reductive cleavage afforded the aldehyde (**3**) in good yield. The Henry reaction of **3** with nitromethane in the presence of 1,1,4,4-tetramethylguanidine[10] led to a diastereomeric mixture of nitro alcohols (**6a** and **6b**) in a 2:1 ratio. Although this diastereomeric ratio could not be improved under various reaction conditions examined,[11] treatment of a mixture of **6a** and **6b** with chlorotimethylsilane and triethylamine at room temperature for 12 h in the presence of catalytic DMAP followed by acidic treatment led to a mixture of cycloadduct **9** (55%) and unreacted **6b** (8%).[12] This result clearly indicates the intervention of the corresponding silyl nitronate (**7**), which underwent [3 + 2] cycloaddition reaction under the given reaction conditions to give the initial adduct (**8**), a direct precursor for **9**. Absolute configuration at the fused sp^3-carbon of cycloadduct **9** was determined to be the one required for the C-5 position of **1** by ^{1}H NMR analysis involving J_{H-H} values and NOE data; selected spin−spin coupling data are listed in Scheme 2.

Such a remarkable kinetic control can be explained by assuming more stable transition states TS_1 (*Z*-nitronate) for **6a** than others shown as TS_2 (*E*-nitronate) for **6a** or both

Scheme 2 [a]

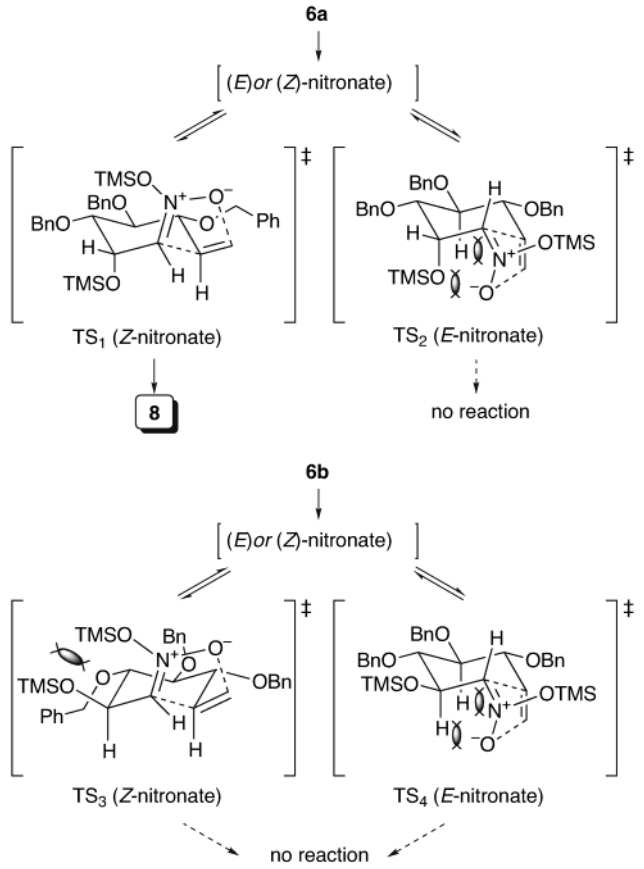


[a] Conditions: (a) BH_3·SMe_2, BF_3·OEt_2, CH_2Cl_2, 0 °C to rt. (b) CBr_4, Ph_3P, CH_2Cl_2, rt, 2 h. (c) Zn, 80% MeOH, reflux, 30 min. (d) CH_3NO_2, 1,1,3,3-tetramethylguanidine, THF, rt, 12 h. (e) TMSCl, Et_3N, DMAP (cat.), THF, rt, 12 h. (f) TsOH, THF, rt, 3 h.

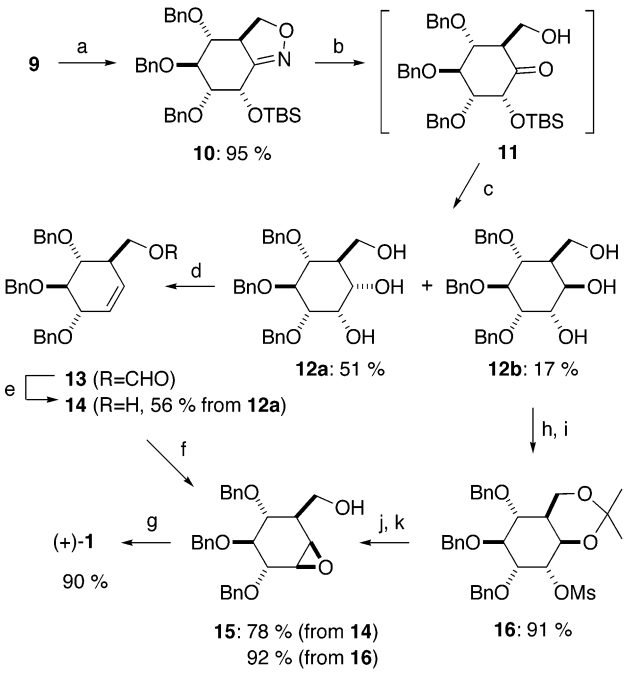
(6) In general, the Ferrier(II) cyclization has been used as a representative means for converting sugars to cyclitol derivatives; see: (a) Ferrier, R. J. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1455−1458; see also *Chem. Rev.* **1993**, *93*, 2779−2831. This reaction can provide a convenient way for converting 6-carbon sugars to 2,3,4,5-(tetrahydoxy)cyclohexanone derivatives. Therefore, if additional substituents are required, they have to be introduced after the cyclization. Since this method features oxy-mercuration as a key step, a more environmentally benign process using promoters other than mercury should be desirable, and some acceptable alternatives become available such as palladium(II)-catalyzed processes. For these works, see: (b) Adam, S. *Tetrahedron Lett.* **1988**, *29*, 6589−6592 and ref 4h. A promising strategy capable of introducing a hydroxymethyl substituent concomitantly on converting a sugar to a cyclitol derivative was developed in Tatsuta's total synthesis of **1** (ref 3). In this case intramolecular nitrile oxide cycloaddition reaction played an important role for a series of transformations from expensive L-glucose to the desired cyclitol derivative.

(7) For generation and intramolecular [3 + 2] cycloaddition reaction of silyl nitronate under the similar conditions, see the preceding paper in this issue. For a review for nitronate cycloadditions including silyl nitronates, see: Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001; pp 267−274.

Scheme 3



Scheme 4 [a]



[a] Conditions: (a) TBDMSOTf, Et_3N, CH_2Cl_2, rt, 12 h. (b) $Mo(CO)_6$, MeCN, 90 °C, 1.5 h. (c) (1) DIBALH, toluene, −78 °C, 30 min, (2) TBAF, THF, rt, 4 h. (d) Trimethyl orthoformate, Ac_2O, 140 °C, 4 d. (e) K_2CO_3, MeOH, rt, 1 h. (f) *m*-CPBA. (g) H_2, Pd−C. (h) Dimethoxypropane, TsOH, THF, rt, 30 min. (i) MsCl, Et_3N, DMAP, THF, rt, 2 h. (j) TsOH, MeOH, rt, 30 min. (k) NaOMe, CH_2Cl_2, rt, 1 h.

TS_3 (*Z*-nitronate) and TS_4 (*E*-nitronate) for **6b** (Scheme 3): TS_3 should suffer from severe $A^{1(3)}$-like steric constraint between the *N*-OTMS and *C*-OTMS groups, whereas TS_2 and TS_4 should suffer from not only such a constraint for the nitronate group but also 1,3-diaxial-like destabilization for the terminal olefin as indicated in Scheme 3. Hence reaction pathways through these three transition states could not lead to cycloadducts at all. It should be pointed out that the geometry of nitronate must be *Z* on the basis of a model as shown in **7** for the cycloaddition reaction to take place. In general, however, the (*E*)-isomer should be more stable thermodynamically than the (*Z*)-isomer for steric reasons. Hence, the (*E*)-isomer must be isomerized to the (*Z*)-nitronate such as **7** under the given reaction conditions.[13]

Conversion of the cycloadduct **9** to **1** is outlined in Scheme 4. The hydroxy group of **9** was protected as a TBDMS ether (**10**). $Mo(CO)_6$-mediated reductive N−O bond cleavege[14] of **10** followed with DIBALH reduction of the resulting keto alcohol **11** in toluene at −78 °C and desilylation afforded a separable mixture of triols (**12a** and **12b**) in a 3:1 ratio.[15]

Hence we turned our attention to converting both triols **12a** and **12b** to the target molecule. Conversion of **12a** to the desired olefin **13** was successful by means of the thermal cleavage of a cyclic ortho ester[16] introduced into the cis-diol part of **12a** on treatment with trimethyl orthoformate (140 °C, 4 d). The formate **13** led to the known intermediate **14** by basic hydrolysis. Epoxidation of **14** to **15** followed by debenzylation provided **1** in good yield, following Trost's procedure.[4j]

(8) Bernet, von B.; Vasella, A. *Helv. Chim. Acta* **1979**, *62*, 1990−2015. A modified procedure for the synthesis of **2** is described in Supporting Information.

(9) Saito, S.; Kuroda, A.; Tanaka, K.; Kimura, R. *Synlett* **1996**, 231−233.

(10) Simoni, D.; Invidiata, F. P.; Manfredini, S.; Ferroni, R.; Lampronti, I.; Roberti, M.; Pollini, G. P. *Tetrahedron Lett.* **1997**, *38*, 2749−2752.

(11) For related diastereoselective Henry reaction, see: Hanessian, S.; Kloss, J. *Tetrahedron Lett.* **1985**, *26*, 1261−1264. Other bases such as DBU or KF resulted in lower yield with diastereoselectivity lower than that of the TMG-catalyzed case.

(12) No cycloaddition reaction proceeded at all when recovered **6b** was subjected to the same reaction conditions as those for cycloaddition (footnote e in Scheme 2): **6b** was recovered unchanged again in 66%, and the rest of **6b** (34%) seemed to decompose or lead to a mixture of unidentifiable products.

(13) Two possible mechanisms deserve consideration for such a geometrical isomerization of nitronates: one might involve a protonation-deprotonation process and the other might involve the 1,3-migration of a trimethylsilyl group from oxygen to oxygen. For discussion with respect to the 1,3-migration, see: Colvin, E. W.; Beck, A. K.; Bastani, B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1980**, *63*, 697−710.

(14) Nitta, M.; Yi, A.; Kobayashi, T. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 991−994.

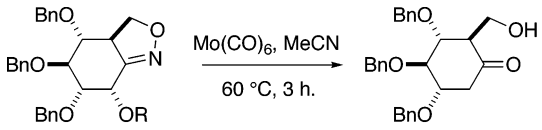
(15) Some other reducing agents employed for this conversion did not effect stereochemical outcomes more selective than that of DIBALH in toluene. For instance, other reducing conditions such as DIBALH/THF, DIBALH/LiCl/THF, $NaBH_4$/THF, $NaBH_4$/LiCl, or $NaBH_4$/CeCl/THF gave less selective results: yields of **12a** and **12b** were 16% and 13%, 22% and 11%, 49% and 20%, 44% and 15%, or 20% and 33%, respectively.

(16) For a review for cleavage of cyclic ortho esters, see: *Org. React.* **1984**, *30*, 457−566.

On the other hand, the minor triol **12b** was uneventfully converted to epoxide **15** by a series of routine reactions involving selective acetonide formation and mesylation to afford **16** (91%), followed by acidic deprotection of the acetonide and the final intramolecular Williamson process to give **15** in very high yield (92% for two steps). Spectroscopic data, melting points, and optical rotations of the synthesized **14**, **15**, and **1** were totally identical with those reported in the literature.[1,3b,4i,j,17]

It should be mentioned that if the above-mentioned protection process (**9** to **10** in Scheme 4) was skipped or a protecting group was not the TBDMS group, the N−O bond cleavage conditions using $Mo(CO)_6$ led to unexpected results. For example, as shown in Scheme 5, when the hydroxy group of **9** was protected as the acetate (**17**) or mesylate (**18**), the deoxygenated product such as **19** was obtained under the given reaction conditions employing $Mo(CO)_6$,[18] whereas it turned out that this transition metal complex was not effective for N−O bond cleavage of oxazolidine **8**, which was recovered unchanged. The less oxygenated cyclitol of this class **19** might be interesting as a synthetic intermediate applicable to other related natural products.

Scheme 5



17 (R=Ac)
18 (R=Ms)

19: 40 % (from **17**)
50 % (from **18**)

In conclusion, we have demonstrated a novel strategy for converting D-glucose to C_6-cyclitol with a hydroxymethyl substituent on the ring. In this transformation, the Henry reaction was crucial because it provided not only a requisite one-carbon but also an important clue for carbocyclization in a single operation. Thus-obtained enantiomerically pure oxazoline-embedded C_7-unit **9** readily led to (+)-cyclophellitol.[19] Although the conversion of **2** to **5** (benzylidene acetal cleavage) or **3** to **6a** (Henry reaction) still remains to be refined in terms of selectivity, the key intermediate **9** is readily available in a gram scale and may be versatile for the synthesis of related natural products. In addition, the potential of the sequential nitroaldol reaction−nitronate cycloaddition process has been well delineated by the present total synthesis. These results might indicate that such a reaction sequence has applications to natural product synthesis in a myriad of contexts.

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Supporting Information Available: Experimental procedures and spectroscopic data for **1**, **2**, **4**−**6**, **9**, **10**, **12**, **14**−**16**, and **19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) All the products gave satisfactory spectroscopic data (NMR, IR, and MS). See Supporting Information.

(18) The generality of $Mo(CO)_6$-mediated deoxygenation reactions of this class is under investigation.

(19) Overall yield of **1** from **9** was 31% corresponding to the sum of two routes via **12a** (19%) and **12b** (12%).