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Synthesis of cyclopropane-annulated conduritol derivatives: norcaran-2,3,4,5-tetraoles

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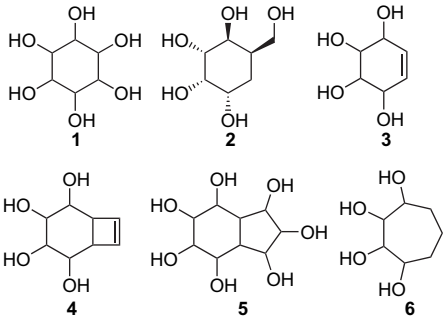
ABSTRACT

Norcaran-2,3,4,5-tetraoles were synthesized starting from methyl 1,3,5-cycloheptatriene-7-carboxylate in several steps. Norcaradiene endoperoxide is the key component; it was obtained by photooxygenation of methyl 1,3,5-cycloheptatriene-7-carboxylate. The other oxygen functionalities are introduced through epoxide ring opening and OsO_4-hydroxylation reactions.

1. Introduction

Cyclitol is a generic term used to describe polyhydroxycycloalkanes. Many biologically important molecules and natural products contain polyhydroxylated carbocycle.[1,2] The inositols (**1**) and their derivatives figure prominently in numerous biological processes (Scheme 1).[3] The best-known carbosugar of natural occurrence is pseudo-α-galactose (**2**).[4] Conduritols (**3**) (six diastereomers designated A–F are known) form the most important class of polyhydroxylated cyclohexanoids and thus there is a great deal of interest about the synthesis of these compounds.[5] Several cyclitols have been used as sweeteners, antibiotics, antiviral, antidiabetes, and anticancer agents.[6] Many analogues and structural variants of **1** and **2** have been synthesized and their biological activities, particularly glycosidase inhibition, have been evaluated.[7,8] The synthesis of polycyclitols like **4**–**6** as new structural variants has recently been achieved.[9] Considering the fundamental importance of cyclitols, we aimed to synthesize the cyclopropane-annulated conduritol analogues.

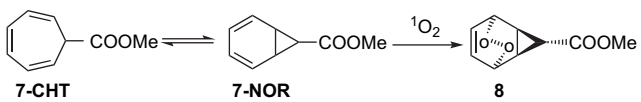


Scheme 1.

2. Results and discussion

Methyl 1,3,5-cycloheptatriene-7-carboxylate (**7**) is the key molecule for our studies. The electron-accepting substituents at C7 in cycloheptatriene (CHT) shift the CHT-norcaradiene (NOR) equilibrium to the norcaradiene side.[10] The CHT-**7** was submitted to photooxygenation using tetraphenyl-porphyrine (TPP) as sensitizer to form NOR-endoperoxide **8** (Scheme 2).[10] To synthesize the norcarane-tetrols, the C=C double bond in the adduct **8** was submitted to an epoxidation reaction with *meta*-chloroperbenzoic acid (*m*-CPBA). Unfortunately, when epoxidation of **8** under various conditions (room temperature or refluxed in CH_2Cl_2 or $CHCl_3$ and ultrasonic bath) was attempted, we isolated, in all cases, only unreacted starting material **8** instead the desired epoxide, which could be a precursor of the NOR-tetroles.

In order to obtain our target molecules, as an alternative route, the endoperoxide **8**, obtained in quantitative yield, can be readily converted to the corresponding *cis*-diacetate **9b** by thiourea reduction at room temperature followed by acetylation with excess acetic anhydride in pyridine (Scheme 3). Later, the various reactions of the diacetate **9b** were investigated. To investigate the introduction of the two hydroxyl groups in a cis configuration to the double bond in *cis*-1,4-diacetoxy-norcaren **9b**, we treated the



Scheme 2.

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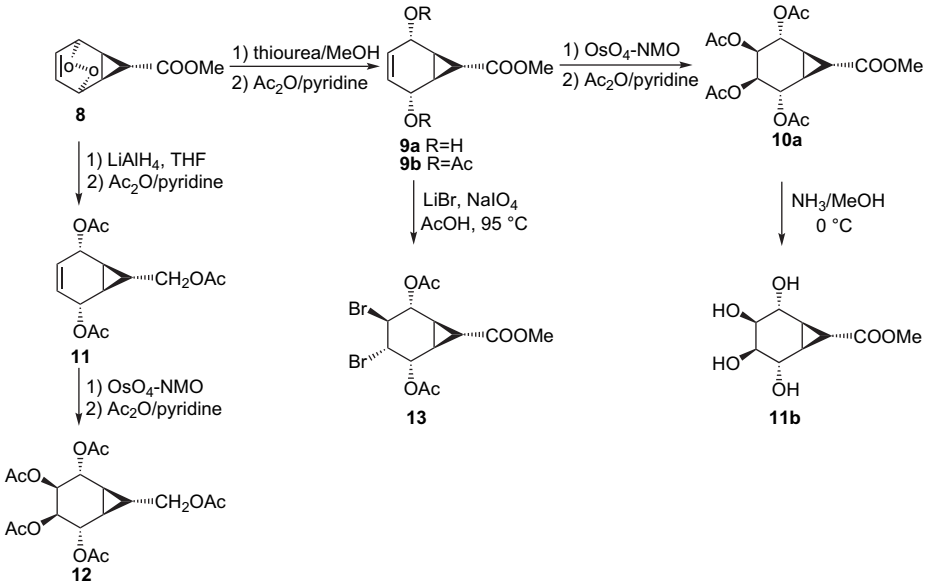


Scheme 3.

diacetate **9b** with catalytic OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant. After the reaction was complete, the crude product was characterized by acetylating with acetic anhydride–pyridine. Since the two faces of the alkene unit in **9b** are not equivalent, isomeric cis-hydroxylation products can be expected. The ^{1}H and ^{13}C NMR spectra of the acetylation product **10a** revealed that only one hydroxylation product instead of the two symmetrical products expected were formed in 94% yield (Scheme 3). For the observed stereoselectivity, we assumed that the cis-hydroxylation occurs from the cyclopropane side due to the lower steric hindrance. The molecular structure of **10a** was established by X-ray diffraction analysis (Fig. 1). Compound **10a** crystallizes in monoclinic space group $P21/c$ (no.: 14) with four molecules in the unit cell. The cyclohexane ring is in a 'twist-chair' conformation, and the puckering parameters of this ring are Q=0.479(3) Å, θ=49.1(4)°, and φ=261.4(4)°, as calculated according to Cremer and Pople.[11] The cyclopropane ring is approximately an equilateral triangle, its bond angles are about 60°, and C–C bond lengths range from 1.499(4) to 1.513(4) Å. The C7 atom, however, is involved in a weak H-bond with the O7 atom of OAc. Furthermore, the endoperoxide **8** was reduced with $LiAlH_4$ and acetylated with pyridine–Ac_2O and the reduction product **11**, which is triacetate, was submitted to OsO_4-cis-hydroxylation followed by acetylation to yield the pentaacetate **12** in total yield of 7.6% (Scheme 3).

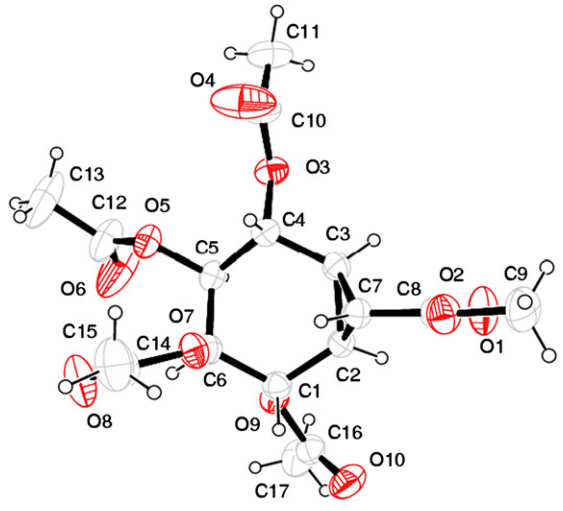
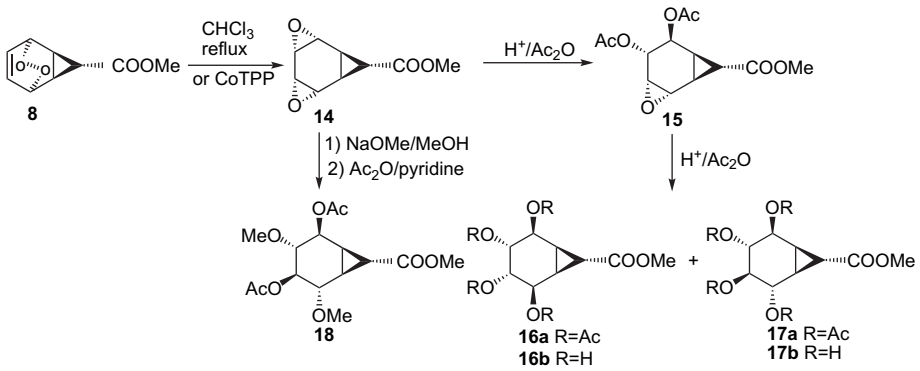


Figure 1. The molecular structure of compound **10a**. Thermal ellipsoids are drawn at the 40% probability level.

In other reactions, so that the different introductions of oxygen on the norcaran skeleton could be examined, diol **9a** or diacetate **9b** was submitted to an epoxidation reaction with peracid to give the corresponding epoxy-diol or diacetate. Probably, the ring opening of epoxide(s) will supply new unsymmetrical tetrol analogue(s) containing a norcaran skeleton. However, the epoxidation reactions did not take place and we isolated the starting material. A Prevost reaction led to generally *anti*-dihydroxylation of an alkene.[12] LiBr efficiently catalyzes the dihydroxylation of alkenes to afford *anti*-diols by using sodium periodate ($NaIO_4$) as oxidant.[12,13] This procedure is a catalytic version of the Prevost reaction. For that reason, we envisioned to prepare the conduritol F structure directly from the diacetate **9b** using a catalytic amount of LiBr (20 mol %) and $NaIO_4$ (30 mol %) in AcOH at 95 °C. The LiBr catalyzed *anti*-dihydroxylation reaction of the diacetate **9b** did not give the expected product. On the other hand, when an excess amount of LiBr–$NaIO_4$ combination was used for the *anti*-hydroxylation, *trans*-dibromo compound **13** was isolated and characterized (Scheme 3). We assumed that the molecular bromine generated in situ from LiBr by oxidation with $NaIO_4$ undergoes bromination with the diacetate **9b** via a bromonium ion to produce *trans*-1,2-dibromodiacetate **13**. It has been reported that sodium periodate oxidatively halogenates a variety of olefins and aromatics with alkali halides as halogen source.[13]

To obtain the cyclopropane-annulated conduritol analogues by the other approach, the norcaradiene endoperoxide **8** was rearranged quantitatively to the corresponding bisepoxide **14** at room temperature with cobalt(II)tetraphenylporphyrin (CoTPP) or by refluxing in chloroform.[10] Bisepoxide **14** was submitted to a sulfuric acid-catalyzed ring-opening reaction in acetic anhydride (Scheme 4). Firstly, we isolated epoxy-diacetate **15**, which was the ring-opening product of one from the two epoxide rings. The structural assignment of **15** was based on ^{3}J coupling assignment in the ^{1}H NMR spectrum, which displayed two different AB systems corresponding to the epoxide ring and diacetate. The observed coupling constants ($^{3}J_{epoxide}$=4.2 Hz and $^{3}J_{diacetate}$=8.5 Hz) in these AB systems are in full agreement with the epoxide and *trans*-diacetate. There was measurable small coupling (^{3}J=1.4 Hz) between the



Scheme 4.

epoxide ring and adjacent acetoxy proton due to nearly 110–120° axial–equatorial dihedral angle. Optimized geometry for the epoxy-diacetate **15** calculated using the AM1 semiempirical method indicated a 117.18° dihedral angle for the vicinal protons concerned (Fig. 2). The measured coupling constant and calculated dihedral angle were completely in agreement with the proposed structure of **15**. When the reaction time was prolonged, column chromatography on silica gel and recrystallization of the reaction mixture afforded the isomeric tetraacetates **16a** and **17a** in a 75:25 ratio (from ^{1}H NMR) as conduritol A and B derivatives, respectively. The ^{1}H and ^{13}C NMR spectra of **16a** showed a symmetrical structure possessing a conduritol A skeleton, whose spectrum is not identical to that of the isolated product from the OsO_4-oxidation. The NMR resonance signals of the other product, **17a**, are completely in agreement with the proposed unsymmetrical structure. The formation of the isomers **16a** and **17a** is reasonably understood in terms of the mechanism outlined in Scheme 5. The cyclopropane-annulated conduritol A skeleton **16a** and conduritol B skeleton **17a** were the expected products in this reaction. The formation of epoxy-diacetate **15** and cyclopropane-annulated conduritol structures **16a** and **17a** are likely explained by the ring opening of the epoxide via the acetoxy group.[14] We assume first that the H^{+} undergoes addition to one of the carbonyl groups of acetic anhydride. The protonating acetic anhydride reacts with one of the epoxides to give acetylated epoxide intermediate **19**. Then, the reaction of the resulting intermediate **19** and acetic acid gives the *trans*-1,2-diacetate-epoxide product **15**. Ring opening of acetylated epoxide intermediate **21** in two different ways (path a and b) gave conduritol analogues **16a** and **17a** (Scheme 5). The ring-opening reaction of bisepoxide **14** with NaOMe gave conduritol B structure **18** as the sole product (Scheme 4).

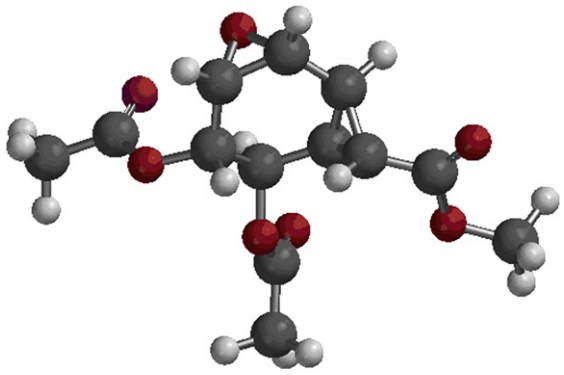


Figure 2. Optimized geometry for the epoxy-diacetate **15** calculated using the AM1 semiempirical method.

To obtain more detailed information about the mechanism of the epoxide ring-opening reactions, we performed some computational calculations. According to our suggested mechanism, the first opening reaction of the bisepoxide **14** can be rationalized in terms of two different product (**15** and **20**) over the acetylated oxonium intermediate **19** (Scheme 5). The geometric optimization showed that the first ring-opening product obtained, **15**, was 2.92 kcal/mol lower in energy than the alternative ring-opening product **20** (Table 1). In an analogous manner we assumed a similar mechanism for the formation of compounds **16a** and **17a**, formed from the opening of the second epoxide ring. The analysis of the reaction products **16a** and **17a** leads to the conclusion that the major pathway involves the intermediate **21** that might be attacked by acetic acid as a nucleophile to form the tetraacetate **16a**. Once again, the calculated results (Table 1) qualitatively support the experimental observations. This could be attributed to the product **16a** being more stable than the unsymmetrical product **17a**.

Finally, deacetylation of **10a** with ammonia in methanol at 0 °C afforded the norcaran-2,3,4,5-tetraole **10b** in high yield (Scheme 3). The deacetylation of **16a** and **17a** as described above gave the free tetrols **16b** and **17b** (Scheme 4).

3. Conclusion

We have described here the synthesis of cyclopropane-annulated conduritol analogues containing a norcaran skeleton starting from methyl 1,3,5-cycloheptatriene-7-carboxylate. The formation mechanism of products was discussed and the experimental and the computational results were compared.

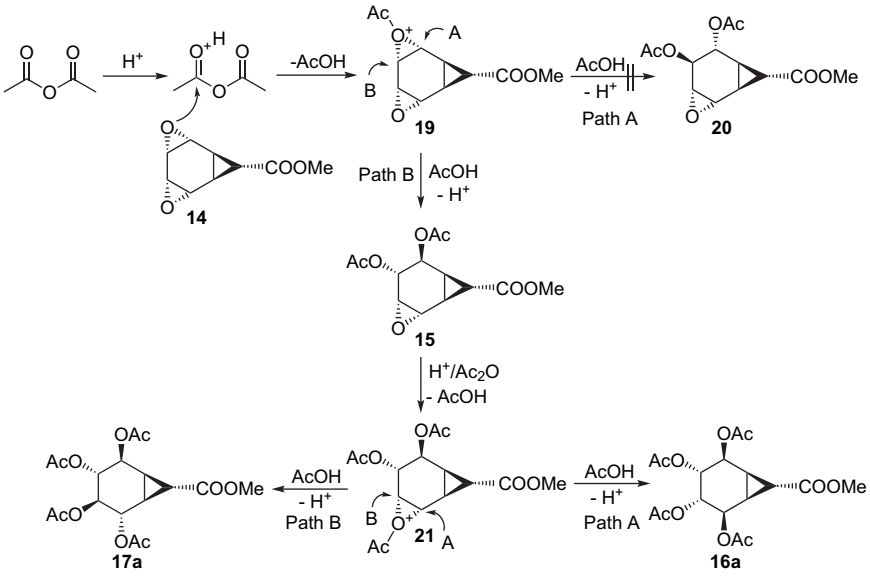
4. Experimental section

4.1. General methods

Solvents were concentrated at reduced pressure. Melting points were determined on a Buchi 539 capillary melting apparatus and are uncorrected. Infrared spectra were recorded on a Mattson 1000 FT-IR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on 200 (50) and 400 (100) MHz Varian spectrometer and are reported in δ units with $SiMe_4$ as internal standard. Elemental analyses were carried out on a Carlo Erba 1108 model CHNS-O analyzer.

4.2. Calculation methods

All calculations were performed using SPARTAN04 software for Windows, version 1.0.0 on a personal computer.[15] Energies were refined using the semiempirical AM1, PM3, MNDO and the density functional theory (DFT) level[16] with hybrid B3LYP/6-31G** basis



Scheme 5. Formation mechanism of **15**, **16a**, and **17a**.

Table 1
Heat of formation of epoxide ring-opening products **15**, **16a**, **17a**, and **20**

Compound	AM1 (kcal/mol)	PM3 (kcal/mol)	MNDO (kcal/mol)	DFT at B3LYP/6-31G** (a.u.)
15	−211.78	−216.65	−202.28	−1031.56
20	−208.86	−214.63	−199.96	−1031.54
16a	−398.45	−375.14	−336.39	−1413.35
17a	−372.10	−372.10	−365.92	−1413.33

sets (Becke's 3 parameter functional[17] with the non-local correlation provided by the expression given by Lee et al.[18]).

*4.2.1. (2R(S),5S(R))-Methyl 2,5-dihydroxybicyclo[4.1.0]hept-3-ene-7-carboxylate (**9a**)*

The endoperoxide **8**[10] (1.00 g, 5.50 mmol) was dissolved in 20 mL of methanol. A solution of thiourea (427 mg, 5.62 mmol) in 5 mL of methanol was then added dropwise over 10 min. After the solution was stirred at room temperature for 6 h, the residue was filtered through filter paper. The solvent was evaporated to give the diol **9a** (yellow oil, 950 mg, 94%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.84 (m, =CH, 2H), 4.58–4.53 (m, OH, 2H), 4.39 (m, OCH, 2H), 3.68 (s, OMe, 3H), 2.01 (d, J=4.4 Hz, X part of AX_2-system, CH, 2H), 1.37 (t, J=4.4 Hz, A part of AX_2-system, CH, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.3, 130.4, 63.8, 54.0, 28.0, 23.2; IR (CH_2Cl_2, cm^{-1}) 3337, 3036, 2954, 2905, 1726, 1452, 1354, 1305, 1204, 1172, 1083, 1044, 1010, 979, 803. Anal. Calcd for $C_9H_{12}O_4$: C, 58.69; H, 6.57. Found: C, 59.08; H, 6.43.

*4.2.2. (2R(S),5S(R))-7-(Methoxycarbonyl)bicyclo[4.1.0]hept-3-ene-2,5-diyl diacetate (**9b**)*

A mixture of 900 mg (4.89 mmol) of **9a**, 2 mL of acetic anhydride, and 3 mL of pyridine was stirred at room temperature for 14 h. Then, the mixture was cooled to 0 °C, added to 50 mL of 4 N HCl, and extracted with CH_2Cl_2 (3×50 mL). The combined organic layer was washed with $NaHCO_3$ (3×20 mL) and water (3×25 mL), and then dried ($MgSO_4$). Removing the solvent under reduced pressure gave **9b** (yellow oil, 1.17 g, 90%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.90 (m, =CH, 2H), 5.47–5.44 (m, OCH, 2H), 3.65 (s, OMe, 3H), 2.08 (s, OAc, 6H), 1.97 (d, J=4.4 Hz, X part of AX_2-system, CH, 2H), 1.44 (t, J=4.4 Hz, A part of AX_2-system, CH, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.2, 172.4, 128.8, 65.7, 54.0, 24.5, 23.1, 22.3; IR (CH_2Cl_2, cm^{-1}) 3056, 2954, 1732, 1534, 1456, 1433, 1371, 1303, 1233, 1173, 1099, 1019, 737. Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.43; H, 6.11.

*4.2.3. (2R(S),3S(R),4R(S),5S(R))-7-(Methoxycarbonyl)bicyclo-[4.1.0]heptane-2,3,4,5-tetrayl tetraacetate (**10a**)*

To a solution of *N*-methylmorpholine *N*-oxide (550 mg, 4.70 mmol) in water (3 mL) was dissolved the solution of diacetate **9b** (884 mg, 3.30 mmol) in acetone (15 mL). After the flask was cooled to −5 °C, OsO_4 (1%, 5 mL) was added under nitrogen and stirred for 18 h without cooling the bath again. $NaHSO_3$ (900 mg), florisil (4 g), and water (4 mL) were added and the slurry was stirred for 8 h. Then, Celite (2 g) was added and the slurry was stirred for 1 h. The mixture was filtered and the solid was washed with acetone (2×50 mL). The solvent was removed under vacuum and then the residue was dissolved in pyridine (5 g) and Ac_2O (3 g). The mixture was stirred at room temperature for 5 days, cooled to 0 °C and poured into a cold solution (1%, 100 mL) of HCl. The mixture was extracted with $CHCl_3$ (3×50 mL). The combined organic layer was washed with $NaHCO_3$ (5%, 100 mL) and water (100 mL), and then dried over Na_2SO_4. After the solvent was evaporated, the tetraacetate **10a** was recrystallized from $CHCl_3$/hexane as white crystals (1.20 g, 94%, mp 183–184 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.17 (d, J=5.5 Hz, A part of AB-system, OCH, 2H), 5.16 (d, J=5.5 Hz, B part of AB-system, OCH, 2H), 3.67 (s, OMe, 3H), 2.10 (s, OAc, 6H), 2.07 (t, J=4.8 Hz, A part of AX_2-system, CH, 1H), 2.03 (s, OAc, 6H), 1.71 (d, J=4.8 Hz, X part of AX_2-system, CH, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 170.0, 169.6, 69.3, 67.8, 52.5, 24.3, 21.3, 21.2, 21.1; IR (CH_2Cl_2, cm^{-1}) 3062, 2962, 1743, 1450, 1373, 1234, 1056, 971, 941, 833, 732. Anal. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74. Found: C, 51.36; H, 5.58.

*4.2.4. (2R(S),3S(R),4R(S),5S(R))-7-(Acetoxymethyl)bicyclo[4.1.0]-heptane-2,3,4,5-tetrayl tetraacetate (**12**)*

To a stirred solution of the endoperoxide **8** (8.60 g, 47.25 mmol) in a dry THF (60 mL) cooled water-ice bath, $LiAlH_4$ (3.50 g, 92.10 mmol) was added portionwise over 30–35 min at 0 °C. After stirring at the same temperature for 2 h, the cold bath was removed and the mixture was stirred at room temperature for 2.5 days. The gray mixture was cooled to 0 °C and hydrolyzed by the addition of methanol and water (1:1). The mixture was filtered (inorganic salts) and the solid was washed with THF (40 mL) and methanol (60 mL). The solvents of the combined organic layer were removed.

The crude product (triol, 4.50 g) was acetylated with pyridine (15 mL) and Ac_2O (13 g) for 3 days. Then, to a solution of *N*-methylmorpholine *N*-oxide (2.80 g, 24.0 mmol) in water (12 mL) was dissolved a solution of the obtained acetylation product (crude, 3.47 g) in acetone (50 mL). After the flask was cooled to −5 °C, OsO_4 (1%, 5 mL) was added under nitrogen and stirred for 20 h without cooling the bath again. $NaHSO_3$ (2 g), florisil (6 g), and water (8 mL) were added and the slurry was stirred for 8 h. Then, Celite (4 g) was added and the slurry was stirred for 1 h. The mixture was filtered and the solid was washed with acetone (3×50 mL). The solvent was removed under vacuum and then the residue (1.58 g) was acetylated in pyridine (5 g) and Ac_2O (3 g) for 2 days. Then the mixture was cooled to 0 °C and poured into a cold solution (1%, 100 mL) of HCl. The mixture was extracted with $CHCl_3$ (3×50 mL). The combined organic layer was washed with $NaHCO_3$ (5%, 100 mL) and water (100 mL), and then dried over Na_2SO_4. After the solvent was evaporated, the pentaacetate **12** was recrystallized from $CHCl_3$/ether as white crystals (1.74 g, 7.6%, mp 116–117 °C). The yield of **12** was calculated as a total according to the endoperoxide **8**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.16 (d, J=5.7 Hz, A part of AB-system, OCH, 2H), 5.12 (d, J=5.75 Hz, B part of AB-system, OCH, 2H), 3.92 (d, J=6.9 Hz, OCH_2, 2H), 2.11 (s, OAc, 6H), 2.07 (s, OAc, 3H), 2.04 (s, OAc, 6H), 1.59 (p, J=6.9 Hz, A part of AX_2-system, CH, 1H), 1.20 (d, J=4.8 Hz, X part of AX_2-system, CH, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 170.2, 169.8, 69.5, 68.6, 66.6, 21.3, 21.2, 21.1, 20.7, 18.7; IR (KBr, cm^{-1}) 3635, 3474, 3025, 2960, 2895, 1745, 1655, 1433, 1371, 1150, 1111, 1083, 1046, 981, 949, 927, 878, 834, 806, 786, 757. Anal. Calcd for $C_{18}H_{24}O_{10}$: C, 54.00; H, 6.04. Found: C, 53.66; H, 5.96.

4.2.5. *(2R(S),3S(R),4S(R),5S(R))-3,4-Dibromo-7-(methoxycarbonyl)bicyclo[4.1.0]heptane-2,5-diyl diacetate (**13**)*

Diacetate **9b** (810 mg, 3 mmol) was dissolved in 5 mL of CH_3COOH and to this solvent were added $NaIO_4$ (2.58 g, 12.06 mmol) and LiBr (1.05 g, 12.07 mmol). After the mixture was refluxed for 24 h, acetic acid was removed. The residue was dissolved by CH_2Cl_2 (100 mL) and the organic phase was washed with saturated $NaHCO_3$ solution (2×50 mL) and water (1×50 mL). The organic phase was dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crystallization of the residue from CH_2Cl_2/hexane gave the *trans*-dibromo compound **13** as colorless crystals (1.20 g, 93%, mp 170–171 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (t, J=3.1 Hz, OCH, 1H), 5.33 (d, J=6.8 Hz, OCH, 1H), 4.31 (ddd, J=10.6, 6.8, 3.1 Hz, A part of AB-system, BrCH, 1H), 4.09 (ddd, J=10.6, 6.8, 3.1 Hz, B part of AB-system, BrCH, 1H), 3.67 (s, OMe, 3H), 2.16 (s, OAc, 3H), 2.12 (s, OAc, 3H), 1.99–1.93 (m, CH, 1H), 1.80–1.74 (m, CH, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 169.9, 169.7, 73.3, 69.1, 52.6, 51.1, 49.6, 25.7, 24.9, 22.5, 21.1, 21.1; IR (KBr, cm^{-1}) 2999, 2955, 1749, 1735, 1454, 1374, 1291, 1223, 1180, 1143, 1114, 1027, 979, 936, 757. Anal. Calcd for $C_{14}H_{18}Br_2O_6$: C, 38.03; H, 4.10. Found: C, 38.41; H, 3.93.

4.2.6. *(2R(S),4R(S),5S(R))-Methyl 5,6-bis(acetyloxy)-3-oxatricyclo[5.1.0.0^{2,4}]octane-8-carboxylate (**15**)*

To a solution of the bisepoxide **14**[10] (2 g, 11 mmol) in 15 mL of Ac_2O was added two drops of concd H_2SO_4. The progress of the reaction was monitored by TLC and stirred magnetically at room temperature for 4 h. Then, the reaction mixture was poured into iced-water and extracted with $CHCl_3$ (3×50 mL). The organic layer was washed with saturated $NaHCO_3$ (2×50 mL) and water (1×50 mL), dried ($MgSO_4$), and evaporated. The product **15** was crystallized from CH_2Cl_2/hexane as white crystals (2.95 g, 95%, mp 120–121 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.42 (dd, J=8.5, 4.2 Hz, A part of AB-system, OCH, 1H), 5.06 (dd, J=8.5, 1.4 Hz, B part of AB-system, OCH, 1H), 3.68 (s, OMe, 3H), 3.55 (td, J=4.2, 1.4 Hz, A part of AB-system, OCH, 1H), 3.19 (d, J=4.2 Hz, B part of AB-system, OCH, 1H), 2.22–2.21 (m, CH, 1H), 2.09 (s, OAc, 3H), 2.07–2.04 (m, CH, 1H), 2.3 (s, OAc, 3H), 2.00–1.90 (m, CH, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.4, 172.5, 172.1, 72.0, 70.4, 55.3, 54.5, 54.2, 26.5, 25.6, 25.0, 22.9, 22.8; IR (KBr, cm^{-1}) 2969, 2927, 2873, 1739, 1725, 1455, 1376, 1311, 1218, 1190, 1059, 1040, 964, 884, 870, 763. Anal. Calcd for $C_{13}H_{16}O_7$: C, 54.93; H, 5.67. Found: C, 54.63; H, 5.58.

4.2.7. *Reaction of syn-bisepoxide **14** with acetic anhydride in the presence of sulfuric acid*

To a solution of the bisepoxide **14** (4 g, 22 mmol) in 20 mL of Ac_2O was added eight drops of concd H_2SO_4 followed by stirring magnetically at room temperature for 24 h. After the acetic anhydride was removed under reduced pressure, the residue was dissolved in $CHCl_3$ (10 mL) and washed with NaOH solution (1%, 2×50 mL) and water (1×50 mL), and dried over $MgSO_4$. The solvent was evaporated and the chromatography of the residue (4.28 g, the ^{1}H NMR analysis of the crude product showed the presence of a mixture of **16a**/**17a** in a ratio of 75:25) on silica gel eluting with ethyl acetate/hexane (7:3) gave the mixture of the product **16a** and **17a** (2.8 g). While the obtained elution mixture was precipitated by ether to give the asymmetric product **17a** (560 mg, 6.6%), the etheric solution provided the symmetrical product **16a** (2.24 g, 26.4%). *(2R(S),3S(R),4R(S),5S(R))-7-(methoxycarbonyl)bicyclo[4.1.0]heptane-2,3,4,5-tetrayl tetraacetate (16a)*: mp 104–105 °C, crystallized from CH_2Cl_2/hexane as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (ddd, J=7.0, 4.7, 2.1 Hz, A part of AB-system, OCH, 2H), 4.97 (dd, J=7.0, 2.1 Hz, B part of AB-system, OCH, 2H), 3.67 (s, OMe, 3H), 2.31 (dtd, J=7.0, 4.7, 2.1 Hz, A part of AX_2-system, CH, 1H), 2.09 (s, OAc, 6H), 2.07 (s, OAc, 6H), 2.01 (t, J=4.7 Hz, X part of AX_2-system, CH, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.1, 170.0, 69.6, 67.6, 52.5, 26.3, 21.1, 21.0, 20.5; IR (KBr, cm^{-1}) 3025, 2957, 1740, 1689, 1448, 1372, 1121, 1067, 1033, 756. Anal. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74. Found: C, 52.75; H, 5.78. *(2R(S),3S(R),4S(R),5R(S))-7-(methoxycar-bonyl)bicyclo[4.1.0]heptane-2,3,4,5-tetrayl tetraacetate (17a)*: mp 142–143 °C, crystallized from CH_2Cl_2/hexane as white crystals. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (dd, J=9.2, 6.6 Hz, OCH, 1H), 5.32 (m, OCH, 1H), 5.04 (d, J=3.3 Hz, OCH, 1H), 4. 67 (dd, J=9.2, 1.5 Hz, OCH, 1H), 3.69 (s, OMe, 3H), 2.35–2.30 (m, CH, 1H), 2.16 (s, OAc, 3H), 2.06 (s, OAc, 3H), 2.04 (s, OAc, 3H), 2.02 (s, OAc, 3H), 1.80–1.78 (m, CH, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.7, 170.4, 170.1, 169.7, 70.0, 69.0, 68.4, 68.1, 52.5, 26.1, 25.1, 23.4, 21.2, 21.0, 20.9, 20.9; IR (KBr, cm^{-1}) 2956, 1748, 1450, 1370, 1227, 1181, 1077, 1036, 931, 760. Anal. Calcd for $C_{17}H_{22}O_{10}$: C, 52.85; H, 5.74. Found: C, 52.90; H, 5.49.

4.2.8. *(2S(R),3R(S),4R(S),5S(R))-3,5-Dimethoxy-7-(methoxycarbonyl)bicyclo[4.1.0]heptane-2,4-diyl diacetate (**18**)*

Metallic Na (1.0 g, 41.6 mmol) was dissolved in dry methanol (60 mL), and then bisepoxide **14** (1.56 g, 8.57 mmol) was added. The mixture was refluxed for 3 days and then cooled to room temperature. The solvent was evaporated and pyridine (20 mL) was added to the residue. The solid was removed by filtration and Ac_2O (15 mL) was added at 0 °C. The mixture was stirred for 3 h at 0 °C and then the cold bath was removed. After the mixture was stirred for 4 h, it was poured into cold HCl solution (1.0%, 150 mL). The mixture was extracted with $CHCl_3$ (3×50 mL). The combined organic layer was washed with $NaHCO_3$ solution (5%, 2×50 mL) and then water (1×50 mL). The solution was dried over Na_2SO_4 and then the solvent was removed under vacuum. The product **18** was crystallized from ether/hexane as white crystals (702 mg, 25%, mp 99–100 °C). ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.95 (dd, J=7.2, 1.4 Hz, OCH, 1H), 4.69 (t, J=8.9 Hz, OCH, 1H), 3.81 (dd, J=8.9, 5.0 Hz, OCH, 1H), 3.65 (s, OMe, 3H), 3.36 (s, OMe, 3H), 3.34 (s, OMe, 3H), 3.21 (dd, J=8.9, 7.2 Hz, OCH, 1H), 2.07 (s, OAc, 3H), 2.06 (s, OAc, 3H), 2.04 (t, J=5.0 Hz, CH, 1H), 1.88 (t, J=5.0 Hz, CH, 1H), 1.63 (ddd, J=7.2, 5.0, 1.4 Hz, CH, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.7, 171.7 (2C), 83.2, 79.7, 74.4, 73.6, 61.7, 58.8, 54.1, 27.5, 26.4, 23.0 (2C), 22.9; IR (KBr,

cm^{-1}) 2987, 2952, 2836, 1747, 1450, 1369, 1291, 1229, 1181, 1159, 1095, 1074, 1032, 996, 969, 1032. Anal. Calcd for $C_{15}H_{22}O_8$: C, 54.54; H, 6.71. Found: C, 54.74; H, 6.78.

4.2.9. (2R(S),3S(R),4R(S),5S(R))-Methyl 2,3,4,5-tetrahydroxybicyclo[4.1.0]heptane-7-carboxylate (**10b**)

Tetraacetate **10a** (320 mg, 0.83 mmol) was dissolved in 50 mL of absolute methanol and the solution was cooled to 0 °C. Dry NH_3 was passed through the solution at the same temperature. Evaporation of methanol and the formed acetamide gave tetrahydroxynorcaran **10b** (170 mg, 94%, recrystallized with methanol as white crystals, mp 121–122 °C). ^{1}H NMR (200 MHz, D_2O) δ 4.01 (d, J=5.2 Hz, A part of AB-system, OCH, 2H), 3.70 (d, J=5.2 Hz, B part of AB-system, OCH, 2H), 3.65 (s, OMe, 3H), 2.10 (t, J=4.8 Hz, A part of AX_2-system, CH, 1H), 1.66 (d, J=4.8 Hz, X part of AX_2-system, CH, 2H); ^{13}C NMR (50 MHz, D_2O) δ 180.6, 76.7, 72.6, 57.0, 31.4, 26.2; IR (CH_2Cl_2, cm^{-1}) 3368, 2975, 2901, 1710, 1667, 1451, 1291, 1203, 1179, 1048, 973, 880, 742. Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.14; H, 6.43.

4.2.10. (2R(S),3S(R),4R(S),5S(R))-Methyl 2,3,4,5-tetrahydroxybicyclo[4.1.0]heptane-7-carboxylate (**16b**)

Compound **16b** was synthesized by ammonolysis of **16a** (240 mg, 0.63 mmol) as described above by the synthesis of **10b**. The tetrol **16b** was crystallized from methanol as white crystals (125 mg, 92%, mp 220–221 °C). ^{1}H NMR (200 MHz, D_2O) δ 4.22 (t, J=5.1, 2.1 Hz, A part of AB-system, OCH, 2H), 3.66 (s, OMe, 3H), 3.48 (d, J=5.1 Hz, B part of AB-system, OCH, 2H), 2.12–2.09 (m, X part of AX_2-system, CH, 2H), 1.97 (t, J=4.4 Hz, A part of AX_2-system, CH, 1H); ^{13}C NMR (50 MHz, D_2O) δ 180.4, 76.5, 71.6, 57.2, 33.1, 24.1; IR (KBr, cm^{-1}) 3391, 2978, 2931, 2031, 1650, 1425, 1415, 1384, 1079, 1048, 880. Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.14; H, 6.32.

4.2.11. (2R(S),3S(R),4S(R),5R(S))-Methyl 2,3,4,5-tetrahydroxybicyclo[4.1.0]heptane-7-carboxylate (**17b**)

Compound **17b** was synthesized by ammonolysis of **17a** (180 mg, 0.47 mmol) as described above by the synthesis of **10b**. The tetrol **17b** was crystallized from methanol as white crystals (97 mg, 95.4%, mp 157–158 °C). ^{1}H NMR (200 MHz, D_2O) δ 4.21 (dd, J=8.9, 6.2 Hz, OCH, 1H), 3.86–3.85 (m, OCH, 1H), 3.77–3.76 (m, OCH, 1H), 3.65 (s, OMe, 3H), 3.15 (dd, J=8.9, 1.6 Hz, OCH, 1H), 2.09–2.1.99 (m, CH, 1H), 1.66–1.63 (m, CH, 2H); ^{13}C NMR (50 MHz, D_2O) δ 180.2, 77.7, 75.6, 73.1, 71.8, 71.7, 57.1, 32.8, 32.5, 27.3, 27.2; IR (KBr, cm^{-1}) 3473, 3061, 2992, 2955, 1724, 1448, 1373, 1313, 1240, 1181, 1036, 992, 969, 737. Anal. Calcd for $C_9H_{14}O_6$: C, 49.54; H, 6.47. Found: C, 49.18; H, 6.25.

4.3. Crystal structure determination

For the crystal structure determination, the single-crystal of the compound **10a** was used for data collection on a four-circle Rigaku R-AXIS RAPID-S diffractometer equipped with a two-dimensional area IP detector. The graphite-monochromatized Mo Kα radiation (λ=0.71073 Å) and oscillation scans technique with $\Delta\omega$=5° for one image were used for data collection. Images for **10a** were taken successfully by varying ω with three sets of different χ and φ values. For each compound 108 images for six different runs covering about 99.8% of the Ewald spheres were obtained. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2>2\sigma(F^2)$. The structure was solved by direct methods using SHELXS-97[19] and non-H atoms were refined by full-matrix least-squares method with anisotropic temperature factors using SHELXL-97.[19] *Crystal data for* **10a**: $C_{17}H_{22}O_{10}$, crystal system, space group: monoclinic, $P21/c$; (no.: 14); unit cell dimensions: a=11.3150(4), b=11.4050(5), c=15.8870(5) Å, β=109.47(2)°; volume: 1932.9(4) $Å^3$; Z=4; calculated density: 1.33 mg/m^3; absorption coefficient: 0.111 mm^{-1}; F(000): 816; θ range for data collection 2.2–30.6°; refinement method: full-matrix least-square on F^2; data/parameters: 5914/249; goodness-of-fit on F^2: 1.027; final R indices [$I>2\sigma(I)$]: R_1=0.080, wR_2=0.203; R indices (all data): R_1=0.159, wR_2=0.248; largest diff. peak and hole: 0.514 and −0.365 e $Å^{-3}$; CCDC-675584.

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References and notes

1. (a) Ogawa, S. In *Carbohydrate Mimics*; Chapleur, Y., Ed.; Wiley-VCH: Weinheim, 1998; p 87; (b) Kummeter, M.; Kazmaier, U. *Eur. J. Org. Chem.* **2003**, 3325; (c) Last review for cyclitols: Gültekin, M. S.; Çelik, M.; Balci, M. *Curr. Org. Chem.* **2004**, *8*, 1159.
2. (a) Ogawa, S. *Carbohydrates in Drug Design*; Witezak, Z. J., Nieforth, K. A., Eds.; Dekker: New York, NY, 1997; p 433; (b) Bleriot, Y.; Giroult, A.; Mallet, J.-M.; Rodriguez, E.; Vogel, P.; Sinay, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2553.
3. (a) Balci, M.; Sütbeyaz, Y.; Seçen, H. *Tetrahedron* **1990**, *46*, 3715; (b) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. J. *Chem. Rev.* **1996**, *96*, 1195; (c) Suami, T. *Pure Appl. Chem.* **1987**, *59*, 1509; (d) Balci, M. *Pure Appl. Chem.* **1997**, *69*, 97; (e) Mehta, G.; Mohal, N.; Lakshminath, S. *Tetrahedron Lett.* **2000**, *41*, 3505.
4. (a) Berridge, M. J. *Nature* **1993**, *361*, 315; (b) Hudlicky, T.; Restrepo-Sanchez, N.; Kary, P. D.; Jaramillo-Gomez, L. M. *Carbohydr. Res.* **2000**, *324*, 200.
5. (a) Carless, H. A. *Tetrahedron: Asymmetry* **1992**, *3*, 795; (b) Johnson, C. R. *Acc. Chem. Res.* **1998**, *31*, 333; (c) Landais, Y. *Chimia* **1998**, *52*, 104.
6. Reviews: (a) Heightman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750; (b) Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605; (c) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21; (d) Suami, T. *Top. Curr. Chem.* **1990**, *154*, 257.
7. (a) Mehta, G.; Reddy, D. S. *Tetrahedron Lett.* **1999**, *40*, 9137; (b) Mehta, G.; Reddy, D. S.; Ramesh, S. S.; Tatu, U. *Tetrahedron Lett.* **1999**, *40*, 9141; (c) Mehta, G.; Ramesh, S. S. *Chem. Commun.* **2000**, 2429.
8. For a few related examples of syntheses of annulated conduritols, see: (a) Billington, D. C.; Perron-Sierra, F.; Picard, I.; Beaubras, S.; Duhault, J.; Espinal, J.; Challal, S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2307; (b) Kara, Y.; Balci, M.; Bourne, S. A.; Watson, W. H. *Tetrahedron Lett.* **1994**, *35*, 3349; (c) Desjardins, M.; Lallemand, M. C.; Hudlicky, T.; Abboud, K. A. *Synlett* **1997**, 728; (d) Boyer, F.-D.; Lallemand, J.-Y. *Synlett* **1992**, 969; (e) Dookhun, V.; Bennet, A. J. *Can. J. Chem.* **2004**, *82*, 1361; (f) Banwell, M. G.; Collis, M. P.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1913; (g) Banwell, M. G.; Corbett, M.; Mackay, M. F.; Richards, S. L. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1329; (h) Boyer, F.-D.; Lallemand, J.-Y. *Tetrahedron* **1994**, 10443.
9. (a) Kelebekli, L.; Kara, Y.; Balci, M. *Carbohyd. Res.* **2005**, *340*, 1940; (b) Kara, Y.; Balci, M. *Tetrahedron* **2003**, *59*, 2063; (c) Goverdan, M.; Senaiar, S. R. *Tetrahedron Lett.* **2001**, *42*, 1987; (d) Sengul, M. E.; Menzek, A.; Saracoglu, N. *J. Chem. Res.* **2005**, 382.
10. (a) Adam, W.; Balci, M.; Pietrzak, B. *J. Am. Chem. Soc.* **1979**, *101*, 6285; (b) Balci, M. *Turk. J. Chem.* **1992**, *16*, 42; (c) Adam, W.; Balci, M.; Rivera, J. *Synthesis* **1979**, 807.
11. Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354.
12. (a) Cambie, R. C.; Rutledge, P. S. *Org. Synth.* **1980**, *59*, 169; (b) Emmanuvel, L.; Shaikh, T. M. A.; Sudalai, A. *Org. Lett.* **2005**, *7*, 5071.
13. Dewkar, G. K.; Narina, S. V.; Sudalai, A. *Org. Lett.* **2003**, *5*, 4501.
14. See for epoxide ring reactions: (a) Yadollahi, B.; Esfahani, F. K. *Chem. Lett.* **2007**, *36*, 676; (b) Das, B.; Reddy, V. S.; Tehseen, F. *Tetrahedron Lett.* **2006**, *47*, 6865; (c) Fan, R.-H.; Hou, X.-L. *Tetrahedron Lett.* **2003**, *44*, 4411; (d) Dalpozzo, R.; De Nino, A.; Nardi, M.; Russo, B.; Procopio, A. *ARCIVOC* **2006**, *vi*, 67; (e) Ramesh, P.; Reddy, N.; Venugopal, D.; Subrahmanyam, M.; Venkateswarlu, Y. *Synth. Commun.* **2001**, *31*, 2599.
15. *Spartan v. 5.0*; Wave function: 18401 Von Karman Avenue, Suite 370, Irvine, CA 92612, 2003.
16. Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, NY, 1994.
17. Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.
18. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.
19. Sheldrick, G. M. *SHELXS97 and SHELXL97*; University of Göttingen: Göttingen, Germany, 1997.