AAA in KAT/DYKAT Processes: First- and Second-Generation Asymmetric Syntheses of (+)- and (−)-Cyclophellitol

Barry M. Trost,* Daniel E. Patterson, and Erik J. Hembre[a]

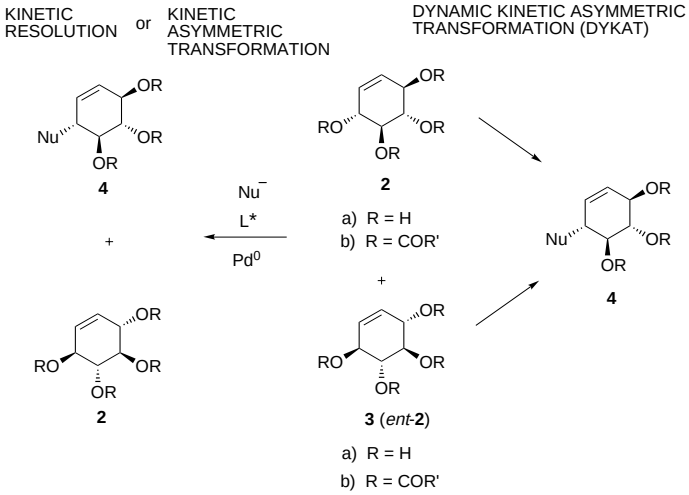
Abstract: Kinetic resolutions and kinetic asymmetric transformations (KAT) as well as dynamic kinetic resolutions and dynamic kinetic asymmetric transformations (DYKAT) are important synthetic protocols. The feasibility of KAT and DYKAT processes for asymmetric allylic alkylations (AAA) is explored utilizing a single substrate – conduritol B tetraesters. Both processes can be performed resulting in excellent enantioselectivity. The impact of nucleophile and leaving group on the effectiveness of each is outlined. The ability to differentiate the various hydroxyl groups is also described. For this purpose, 4-*tert*-butyldimethylsiloxy-2,2-dimethylbutyric acid was developed as a nucleophile. The utility of effecting KAT/DYKAT processes through the Pd-catalyzed AAA reaction is demonstrated by efficient syntheses of both enantiomers of the potent glycosidase inhibitor cyclophellitol.

Keywords: allyl complexes · asymmetric catalysis · natural products · palladium · total synthesis

Introduction

Glycosidase inhibitors not only aid in the understanding of glycoprotein processing but also may find applications in immunology, diabetes, virology, and cancer. Cyclophellitol (**1**), first isolated in 1990 from the mushroom *Phellinus* sp.,[1] has shown activity as an inactivator of β-glucosidase and an inhibitor of HIV.[2] Because of its potent biological activity, cyclophellitol has been the focus of extensive synthetic effort. However, to date most syntheses start with enantiomerically pure natural products, most notably carbohydrates.[3] Such strategies frequently engender long synthetic sequences due to the need to manipulate functionality largely by the use of protecting groups. In addition, these strategies only provide access to one enantiomer of the natural product. In contrast, de novo asymmetric syntheses can provide the flexibility to access either enantiomer, and often lead to more efficient strategies. Only one asymmetric synthesis of cyclophellitol from achiral starting materials employing a chiral auxiliary has been reported.[4] Herein, we report a first-[5] and a second-generation asymmetric synthesis of cyclophellitol based on the palladium-catalyzed asymmetric allylic alkylation (AAA) of racemic conduritol tetraesters.[6]

Conduritols, the various stereoisomers of 3,4,5,6-tetrahydroxylated cyclohexene, represent multifunctional starting materials of growing importance.[7] The symmetry of conduritol B (**2a** and **3a**) makes it a particularly interesting asymmetric building block.[8] As a chiral racemic substance, a kinetic resolution is feasible (see Scheme 1). Since a benefit



Scheme 1. Methods for de-racemization of conduritols B.

of the AAA process[9] is incorporation of the enantiomeric discriminating step as one of the other bond forming events, thereby reducing the overall number of required steps, the process would be more properly referred to as a kinetic asymmetric transformation (KAT). Thus, the desired product

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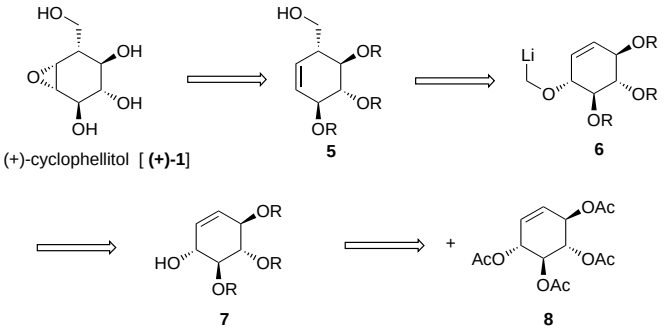
is not the resolved starting material (e.g. **2**) but the enantiomerically enriched product (e.g. **4**) of the chemical transformation. However, since ionization to a π-allylpalladium intermediate generates a complex bearing a plane of symmetry, it is possible to also envision both enantiomers of the substrate reacting to form an enantiomerically pure product (e.g. **4**), a process termed a dynamic kinetic asymmetric transformation (DYKAT). In realizing this scheme, the less reactive enantiomer of **2** or **3** must react faster than the product **4**, which still bears an allyl ester, reacts further.[10] The advantage of this latter process, if achievable, is obvious—the theoretical yield of the desired enantiomer of the product is now 100% rather than 50% for a KAT. In this paper, we explore both strategies for the synthesis of cyclophellitol.

First generation: Our initial retrosynthesis of (+)-cyclophellitol is shown in Scheme 2.[5] As depicted, cyclophellitol would be available through a hydroxyl-directed epoxidation of a

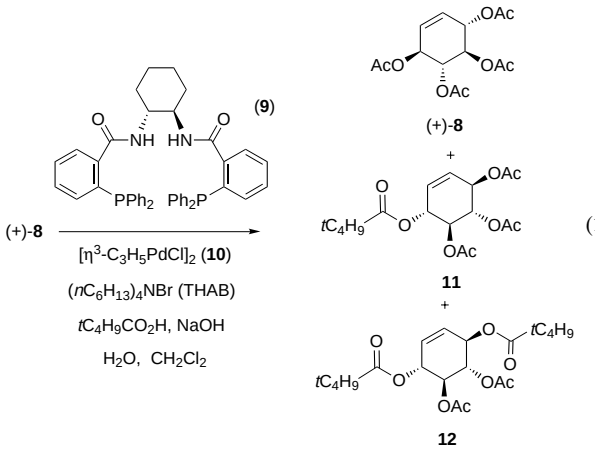


Scheme 2. First-generation retrosynthesis of (+)-cyclophellitol.

suitably protected homoallylic alcohol **5**, which would result from a 2,3-Wittig rearrangement of **6**, available from the selectively protected conduritol B derivative **7**. Enantiomerically enriched conduritol B derivative **7** would come from the palladium-catalyzed kinetic resolution of conduritol B tetraacetate **8**.[6]

A palladium catalyzed kinetic resolution of the racemic C_2-symmetric tetraacetate is possible using the chiral ligand (*R*,*R*)-**9** and a Pd source such as **10**, since, with respect to the ligand, one enantiomer of **8** would provide a "matched" substrate for ionization while the other would be "mismatched" (see e.g. **2**). A pivalate was chosen as the carboxylate nucleophile for the resolution because the resulting allyl pivalate was anticipated to ionize much more slowly that the starting material, and the pivalate should provide a means for easy differentiation of the alcohol protecting groups later on. A potential problem at this stage is the further reaction of monopivalate **11** to provide the dipivalate **12**. Due to the C_2 symmetry of the system, the remaining allyl acetate in **11** is also "matched" for ionization with respect to ligand **9**. The second ionization requires the catalyst to complex the face of the double bond *cis* to the pivalate substituent. The steric bulk of the pivalate was anticipated to hamper this undesired ionization.

The tetraacetate **8** was synthesized in three steps from benzoquinone by a simple modification of the procedure of Guo et al.[6] In our modification, the diacetate of the dibromodiol was formed with acetic anhydride and potassium carbonate to which was added acetic acid and heating to produce the tetraacetate in a one-pot operation. [Eq. (1)] and Table 1 summarizes our results.



(1)

Using our standard ligand **9**[11] in a two phase water/methylene chloride solvent system, the initial reaction using 5 mol% **10** led mainly to a mixture of recovered tetraacetate **8**, monopivalate **11**, and only a small amount of the dipivalate **12** (entry 1). Reducing the catalyst loading in the same period of time did further minimize the formation of dipivalate (entries 2 and 3) although, with 1 mol% **10**, there was more

Table 1. KAT of racemic conduritol B tetraacetate.

Catalyst **10**	**9**	equiv	equiv	M			Yield [% *ee*][a]		
	Mol%	Mol%	$tC_4H_9CO_2H$	NaOH	conc.	*t*[h]	(+)-**8**	**11**	**12**
1	5	15	1.5	1.25	0.4	12	31	39	8
2	2.5	7.5	0.75	0.65	0.4	12	39	42	22
3	1	3	0.75	0.65	0.4	12	63	27	–
4	1	3	0.80	0.65	0.5	24	50	44	1
							(88, 99[b])	(97)	
5	0.5	3	0.80	0.65	0.5	8	53	43	
							(68)	(97)	
6	0.5	1.5	0.80	0.65	0.5	36	74	21	
							(30)	(99)	
7	0.5	1.5	0.80	0.65	1.0	24	54	39	
							(46)	(98)	

[a] % *ee* determined by chiral HPLC analysis using a Chiracel AD column. [b] % *ee* after one recrystallization from diethyl ether/petroleum ether.

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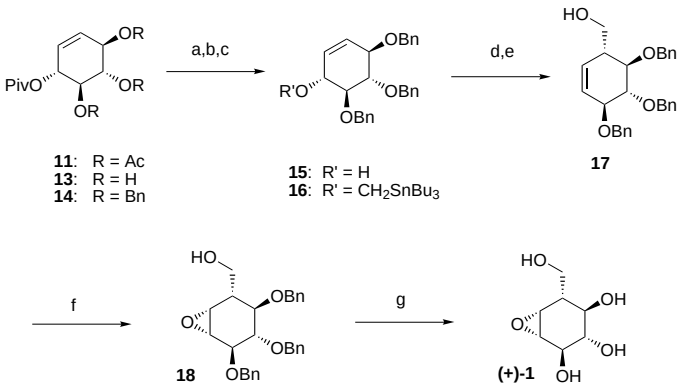
unreacted starting material than would be expected for a kinetic resolution (entry 3). As a result, the concentrations of all of the reactants as well as the time was increased. In this case (entry 4), an excellent result ensued. The reaction stopped at 50% conversion to produce a quantitative yield (based upon a 50% theoretical yield) of recovered tetraacetate of 88% *ee* and an 88% yield (based upon a 50% theoretical yield) of monopivalate **11** of 97% *ee*. In the case of the recovered tetraacetate (+)-**8**, the *ee* increased to 99% after one recrystallization from diethyl ether/petroleum ether. Decreasing the reaction time to 8 h (entry 5) led to incomplete reaction as revealed by recovery of more than the theoretical amount of tetraacetate for a kinetic resolution and the diminished *ee* of the recovered tetraacetate. Further lowering of the catalyst load (entries 6 and 7) also led to incomplete reactions. In all of the incomplete reactions, the *ee* of the product **11** was excellent (97–99% *ee*) as was expected.

With the availability of the monopivalate of 97–99% *ee* almost quantitatively in a KAT, the stage was set for the first-generation synthesis of cyclophellitol as outlined in Scheme 3.

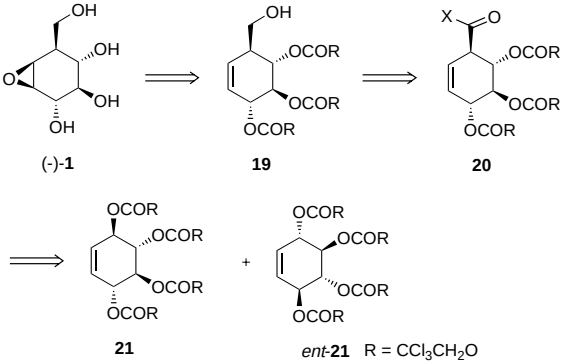


Scheme 3. First-generation synthesis of (+)-cyclophellitol. a) NH_4OH/MeOH, room temperature, 95%; b) BnBr, Bu_4NI, KH, DME, 79%; c) DIBAL-H, CH_2Cl_2, −78 °C, 90%; d) KH, Bu_3SnCH_2I, DME, 0 °C, 88%; e) *n*BuLi, THF, −78 °C, 72%; f) MCPBA, CH_2Cl_2, 0 °C, 78%; g) H_2 (1 atm), $Pd(OH)_2$/C, CH_3OH, room temperature, 90%.

Introduction of the last remaining carbon through the equivalent of an S_N2' with retention of configuration envisioned employment of a 2,3-sigmatropic rearrangement.[12]

Cleavage of the acetates of **11** in the presence of the pivalate was straightforward with ammonium hydroxide in methanol, whereby triol **13** was obtained in 95% yield. Protection of the triol as the benzyl ethers as in **14**, followed by pivalate cleavage afforded alcohol **15**, which could be converted to the corresponding tin derivative **16**. The stage was set for the 2,3-sigmatropic rearrangement, which was accomplished by treatment of **16** with *n*-butyllithium to put the hydroxymethyl group in place with correct regio- and diastereochemistry, to afford **17**. Epoxidation with MCPBA, directed by the homoallylic alcohol, gave a 78% yield of the desired epoxide **18** with a 7% yield of the diastereomeric epoxide. Comparison of the spectral data for **18** with that reported in the literature[3k] confirmed the stereochemistry as depicted. Completion of the synthesis by the published hydrogenation procedure[3k] gave (+)-cyclophellitol (**1**); its physical and spectral properties are in full agreement with the natural product.

Second generation: Replacing a KAT by a DYKAT has the ability to improve the efficiency of any synthesis. Conduritol B constitutes a particularly favorable starting material for such a change in strategy as pointed out in Scheme 1. Realization of a DYKAT requires 1) the ability of both enantiomers of the starting material, **2b** and **3b**, to react and 2) reaction of both to be faster than further reaction of the allyl ester that remains in the product **4**. Since further ionization of **4** requires coordination of palladium to the face of the double bond *cis* to the newly introduced nucleophile; the steric bulk of the latter may inhibit the further reaction of **4**. Adjustment of the leaving group ability of the carboxylate esters was anticipated to overcome this hurdle. Scheme 4



Scheme 4. Second-generation retrosynthesis of (−)-cyclophellitol.

outlines a second-generation retrosynthetic analysis. As previously, the olefin **19** is anticipated to be the immediate precursor, but the hydroxylmethyl group is projected to be introduced in the initial enantiodiscriminating step in the form of a carboxylic acid equivalent (as in **20**) using a DYKAT of racemic **21**. To achieve the DYKAT, the sluggishness of the mismatched ionization experienced with the tetraacetate had to be overcome. We, therefore, turned to the trichloroethyl carbonate (Troc) leaving groups. The success of phenylsulfonylnitromethane[13] as an alkoxycarbonyl anion equivalent[14] led to its use in this sequence.

The Troc-tetraester **21** was prepared in two steps from the tetraacetate–base hydrolysis [$(C_2H_5)_3N$, CH_3OH, H_2O, r.t.] followed by treatement with Troc-chloride. Reaction of racemic **21** ($R = CCl_3CH_2O$) with the sodium salt of (phenylsulfonyl)nitromethane **22**, 2.5% $[dba_3Pd_3]\cdot CHCl_3$ and 7.5% **9** in THF at room temperature gave the desired mono-adduct **23** in 81% yield [Eq. (2)]. The presence of a diastereomeric pair due to the side chain made determination of *ee* at this stage difficult; thus, it was postponed. Complete conversion observed in this reaction indicates that the chiral palladium catalyst can ionize both enantiomers of (+)-**21**, and convert them to a single enantioenriched product.

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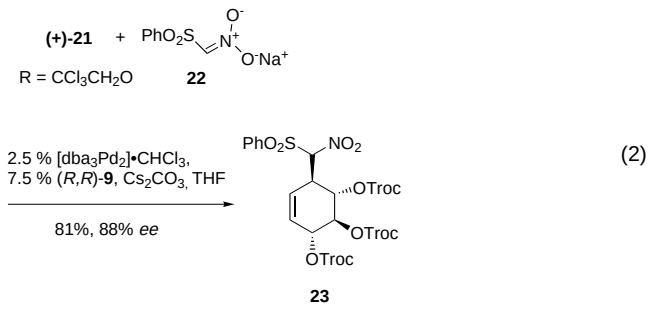
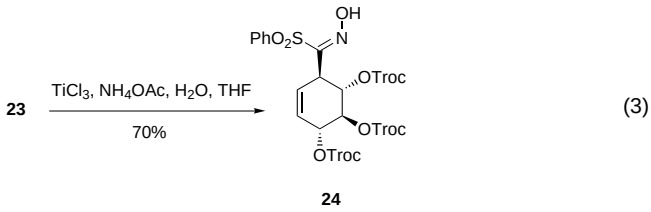


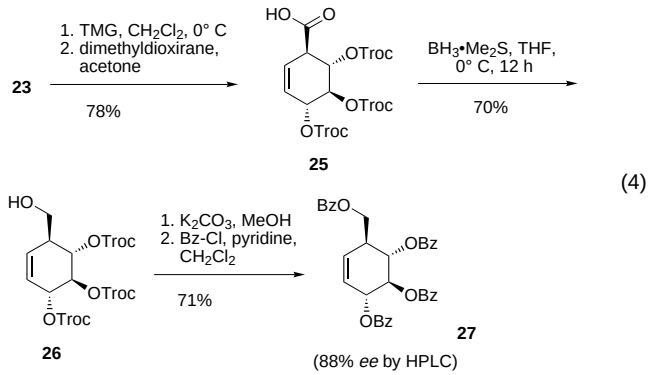
(2)

Several methods to convert **23** to the corresponding acid or ester were examined. Treatment of the nitronate salt of **23** with TBA-oxone,[15] or oxone[16] gave mainly decomposition products, or no reaction. Treatment with CAN,[17] also led to decomposition, along with traces of the corresponding α,β-unsaturated acid. These methods may have led to decomposition through conversion to the desired ester, followed by deprotonation, elimination of the carbonates, and aromatization. Simple hydrolysis of the carbonates may have also contributed to the decomposition products. Treatment with titanium trichloride[18] also did not give the desired ester, but, instead, gave the phenylsulfonyl oxime **24** which didn't react further [Eq. (3)].



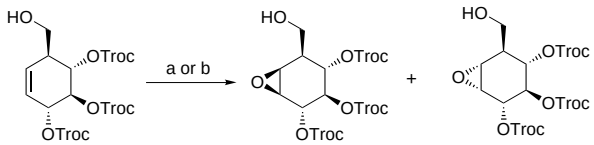
(3)

The mildness of dioxiranes[19] as oxidants led to examination of this method to convert nitrosulfone **23** to the corresponding carboxylic acid **25**. Treatment of **23** with *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG) to form the nitronate salt, followed by reaction with dimethyldioxirane in acetone afforded the desired acid **25** in 78% yield. Interestingly, the double bond of **23** or **25** was unreactive to dimethyldioxirane, as the corresponding epoxide was never observed. Carboxylic acid **25** was then reduced in the presence of the carbonates by treatment with borane/dimethyl sulfide to provide the desired alcohol **26** in 70% yield [Eq. (4)]. At this point the enantiomeric excess of the product could be determined. Alcohol **26** was converted to the corresponding tetrabenzoate **27** which could be separated via chiral HPLC to establish the enantiomeric excess of the palladium reaction as 88%.



(4)

Conversion of **26** into cyclophellitol required epoxidation directed by the homoallylic alcohol. This olefin was expected to be fairly unreactive toward electrophilic epoxidation because of the electron withdrawing allylic carbonate. Treatment with peracids (MCPBA, trifluoroperacetic acid, or 3,5-dinitroperbenzoic acid[20]) at room temperature confirmed the unreactive nature of **26**, giving no reaction or even traces of product. Reaction with peracids at higher temperature (with added radical inhibitor) caused only decomposition. Treatment with vanadium acetylacetonate/hydrogen peroxide caused decomposition, while titanium isopropoxide/hydrogen peroxide[21] returned mainly starting material with only traces of the desired epoxide. Reaction of **26** with dimethyldioxirane proceeded at room temperature to give the desired epoxides (**28** and **29)** in good yield, but with no facial selectivity [Eq. (5)].



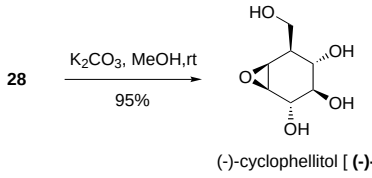
(5)

a: dimethyldioxirane, acetone room temperature.	30%	30%
b: MTO, H_2O_2 (30% aqueous), CH_2Cl_2, room temperature	65%	15%

The known efficiency of rhenium-catalyzed epoxidation of electron poor olefins,[22] led to its investigation for the epoxidation of **26**. Reaction of **26** with methylrhenium trioxide (MTO) and urea/hydrogen peroxide addition complex[23] in methylene chloride gave a low yield ($< 20\%$) of the desired epoxide, but with a reasonable diastereoselectivity of 3:1. Some reports claimed that the rhenium catalyst is more reactive using hydrogen peroxide as the oxidant in a biphasic (methylene chloride/water) system with added pyrazole, pyridine or cyanopyridine as a co-catalyst.[22a, 24] The basic co-catalyst is thought to both protect the product epoxide from acid-catalyzed ring opening, and to stabilize the catalyst. Reaction of **26** under these conditions, however, decreased the yield of the desired epoxide. When the reaction was carried out without added base, using 10% rhenium catalyst, the conversion increased, giving complete conversion to the desired epoxide as a 3.5:1 diastereomeric mixture favoring the desired diastereomer **28**. The diastereomers could be separated to give a 65% isolated yield of the desired epoxide **28** along with 15% of the undesired epoxide **29** [Eq. (5)]. The major diastereomer derived from hydroxyl-directed epoxidation,[25] which was confirmed by conversion of **28** to the enantiomer of the natural product.

The trichloroethyl carbonates of the major epoxide **28** were hydrolyzed by treatment with potassium carbonate in methanol to give a 95% yield of (−)-cyclophellitol (**1**) with a full

agreement of the physical and spectral properties (except for the optical rotation) with the natural product [Eq. (6)]. At this point the enantiomeric excess could be improved to 99% by a single recrystallization from water.

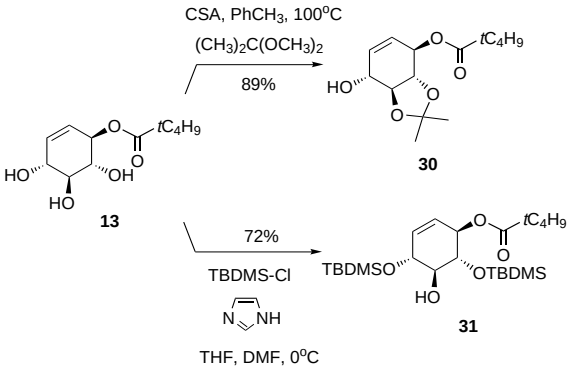


(-)-cyclophellitol [**(-)-1**] (6)

Discussion and Conclusion

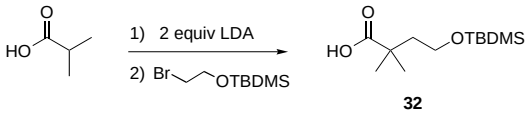
The versatility of the palladium-catalyzed AAA reaction stems from the myriad of methods for introducing chirality.[9] Kinetic resolutions and kinetic asymmetric transformations still constitute an important strategy. On the other hand, dynamic kinetic resolutions and asymmetric transformations are intrinsically more efficient. Conduritol B allows exploitation of both strategies and demonstrates the effectiveness of both with the same substrate.

With the "standard" ligand **9**, the kinetic resolution/KAT was nearly perfect. The resolved tetraacetate (+)-**8** was recovered quantitatively (50% maximum yield) in 83% *ee* which was increased to 99% *ee* with one recrystallization. The transformed tetraester **11** of 97% *ee* was formed in 88% yield. The latter tetraester provides not only a resolution but also a differentiation among the hydroxyl groups. For example, removal of the esters proceeds straightforwardly with base to triol **13** (see Scheme 3). The pivalate provides a steric differentiation of the triol moiety permitting formation of the acetonide **30**. Alternatively, the two hydroxyl groups *anti* to the pivalate may be preferentially protected as silyl ethers to give a 10:1 mixture of **31** and the 5,6-bis-silyl ether from which **31** is isolated pure in 72% yield [Eq. (7)]. The position of the silyl groups, as depicted, is readily discerned in the ^{1}H NMR spectrum. Correlation experiments indicate the signal at $\delta = 3.55$ corresponds to H^5. This signal also shows vicinal coupling to the OH proton.

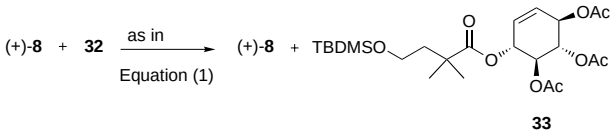


(7)

A novel pivalate-like carboxylic acid **32** was designed to allow reverse order of ester cleavage. Its synthesis involves quenching the dianion derived from isobutyric acid with 2-bromoethyl *tert*-butyldimethylsilyl ether [Eq. (8)]. It participates in the exactly analogous fashion in the kinetic resolution/KAT as pivalic acid as summarized in Equation (9).

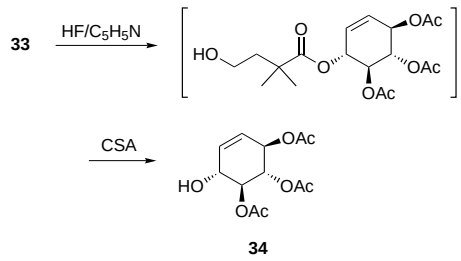


(8)



(9)

In this case, recovered tetraacetate of 87% *ee* was also obtained quantitatively and the mono-pivalate analogue **33** of 95% *ee* was obtained in 88% yield. Exposure of **33** to HF/pyridine only effects desilylation. Acid-catalyzed lactonization completes the removal to form the triacetate **34** [Eq. (10)]. Thus, differentiation among all of the hydroxyl groups of scalemic conduritol B is possible by this approach.



(10)

The first-generation KAT synthesis provided the natural (+)-cyclophellitol in eight steps and 26% overall yield from racemic conduritol B tetraacetate. The unnatural enantiomer (−)-cyclophellitol is equally accessible, only requiring a change in the absolute configuration of the ligand in [Eq. (2)].

By modifying the ester of racemic conduritol B, a dynamic kinetic asymmetric transformation also becomes equally available. With a carbon nucleophile and a trichloroethyl carbonate leaving group, the correct balance of the effectiveness of the leaving group to permit both a "matched" and "mismatched" ionization of the racemic substrate and to prevent further reaction of the enantiomerically enriched monoalkylation product is achieved. Kinetic resolutions and KAT processes are also possible with the Troc-tetraester **11** from which unreacted Troc tetraester of high *ee* can be recovered. Thus, DYKAT is not due to equilibration of the starting tetraester. Its utility is highlighted by the first asymmetric synthesis of (−)-cyclophellitol in five steps in 27% overall yield from racemic tetracarbonate **21**. Obviously, the (+)-enantiomer is equally accessible by simply changing the absolute configuration of the ligand. The unmasking of the phenylsulfonylnitromethane as a carboxy synthon with dimethyldioxirane is noteworthy, especially in light of the failure of our other mild protocols. It is also the first illustration of the ability of the rhenium-catalyzed epoxidation to be stereochemically directed by a homoallyl alco-

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hol.[22–25] These methods should prove useful not only in providing access to this important class of glycosidase inhibitors but more generally to highly functionalized chiral cyclohexane derivatives.

Experimental Section

General methods: See ref. [26].

(−)-(1*R*,2*S*,3*S*,4*R*)-1-Pivaloxy-2,3,4-triacetoxy-5-cyclohexene (11) and **(+)-(1*S*,2*R*,3*R*,4*S*)-1,2,3,4-tetraacetoxy-5-cyclohexene (8)**: A mixture of (±)-1,2,3,4-tetra-*O*-acetylconduritol B (**8**, 1.57 g, 5.0 mmol), pivalic acid (0.408 g, 4.0 mmol), tetrahexylammonium bromide (0.435 g, 1.0 mmol), **10** (19 mg, 0.05 mmol, 1 mol %), and ligand (*R*,*R*)-**9** (105 mg, 0.15 mmol, 3 mol %) was degassed by evacuating and purging with argon (3×). Freshly distilled CH_2Cl_2 (10 mL) was added through an air-tight syringe, followed by a 0.5 M NaOH solution (6.5 mL), which had been previously degassed by purging with argon. The resulting biphasic mixture was stirred vigorously at room temperature. After 16 h, the mixture was washed with, 20 % aq. K_2CO_3 (10 mL) and the aqueous layer extracted with diethyl ether (2×10 mL), the combined organic layers dried ($MgSO_4$), and then filtered through a short plug of silica gel to remove the catalyst. The silica gel was rinsed with diethyl ether (20 mL) and the filtrate was concentrated in vacuo. Chromatography on silica gel (3:1 to 1:1 petroleum ether/diethyl ether gradient) provided the dipivalate (19 mg, 1 %), followed by monopivalate **11** (776 mg, 44 %), followed by tetraacetate (+)-**8** (781 mg, 50 %, 83 % *ee*). Data for **11**: m.p. 110 °C; $[\alpha]_D^{23} = -163.0°$ ($c = 1.11$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.68$ (s, 2H), 5.57 (m, 2H), 5.36 (m, 2H), 2.05 (s, 3H), 2.03 (s, 3H), 2.01 (s, 3H), 1.16 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 177.7$, 170.2, 169.9, 169.6, 127.7, 127.2, 71.6, 71.4, 71.2, 71.0, 38.7, 26.9, 20.8, 20.6, 20.5; IR (neat): $\tilde{\nu} = 2975$, 1758, 1368, 1221 cm^{-1}; elemental analysis calcd (%) for $C_{17}H_{24}O_8$: C 57.30, H 6.79; found: C 57.40, H 7.00; enantiomeric excess determined by HPLC (Chiralcel AD column, eluting with 95:5 heptane/*i*PrOH, 1 mL min^{-1}: (+)-enantiomer $t_R = 7.69$ min, (−)-enantiomer $t_R = 8.48$ min).

(−)-(1*R*,2*S*,3*S*,4*R*)-2,3,4-Tribenzyloxy-1-(tributylstannyl)methoxy-5-cyclohexene (16): Potassium hydride (120 mg, 30 % suspension in mineral oil, 0.89 mmol followed by removal of mineral oil) was suspended in dimethoxyethane (DME) (2.3 mL) at 0 °C. The alcohol **15** (190 mg, 0.456 mmol) was added slowly as a solution in DME (1 mL) and the mixture was warmed to room temperature. After 30 min, the mixture was cooled back to 0 °C and iodomethyltributyltin (287 mg, 0.67 mmol) was added. The mixture was warmed to room temperature. After 45 min, aq. ammonium chloride (10 mL) was added and the mixture was extracted with diethyl ether (2×25 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated in vacuo. Chromatography on silica gel (20:1 to 10:1 petroleum ether/diethyl ether gradient) provided the tributylstannylmethylether **16** (288 mg, 88 %) as a colorless oil. $[\alpha]_D^{23} = -83.9°$ ($c = 1.32$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.4-7.2$ (m, 15H), 5.77 (m, 2H), 5.0–4.8 (m, 4H), 4.71 (ABq, $J = 11.5$ Hz, $\Delta\tilde{\nu} = 16.4$ Hz, 2H), 4.21 (m, 1H), 3.87 (m, 2H), 3.8–3.6 (m, 3H), 1.6–1.4 (m, 6H), 1.4–1.2 (m, 6H), 0.88 (m, 14H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 138.9$, 138.8, 138.4, 128.4, 128.3, 128.3, 128.0, 127.8, 127.7, 127.5, 127.4, 127.3, 85.1, 83.5, 83.1, 80.1, 75.6, 75.3, 72.5, 60.0, 29.1, 27.3, 13.7, 8.9; IR (neat): $\tilde{\nu} = 2924$, 1454, 1069 cm^{-1}.

(+)-(1*S*,2*R*,3*R*,4*R*)-4-Hydroxymethyl-1,2,3-tribenzyloxy-5-cyclohexene (17): *n*-Butyllithium (0.70 mL of a 1.6 M solution in hexanes, 1.13 mmol) was added to a cooled (−78 °C) solution of the stannylmethyl ether **16** (270 mg, 0.375 mmol) in THF (7.5 mL). After 2 h, the reaction was quenched with sat. aq. ammonium chloride (10 mL), warmed to room temperature, and extracted with diethyl ether (3×20 mL). The organic layers were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. Chromatography on silica gel (2:1 to 1:1 petroleum ether/diethyl ether gradient) provided the homoallylic alcohol **17** as a colorless oil (117 mg, 72 %). $[\alpha]_D^{23} = +104.5°$ ($c = 1.92$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.4-7.2$ (m, 15H), 5.76 (dt, $J = 10.0$, 2.5 Hz, 1H), 5.55 (dt, $J = 10.0$, 1.8 Hz, 1H), 5.01 (d, $J = 11.2$ Hz, 1H), 4.94 (s, 2H), 4.70 (s, 2H), 4.66 (d, $J = 11.2$ Hz, 1H), 4.25 (m, 1H), 3.85 (dd, $J = 10.0$, 7.8 Hz, 1H), 3.66 (m, 3H), 2.49 (m, 1H), 1.47 (t, $J = 5.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 138.7$, 138.2, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 85.1, 80.8, 78.5, 75.3, 75.1, 72.1, 63.3, 45.7; IR (neat): $\tilde{\nu} = 3442$, 3030, 2878, 1454, 1359 cm^{-1}; elemental analysis calcd (%) for $C_{28}H_{30}O_4$: C 78.11, H 7.02; found: C 78.33, H 7.15.

(+)-2,3,4-Tri-*O*-benzylcyclophellitol (18): MCPBA (76 mg, 0.44 mmol) was added to a cooled (0 °C) solution of the alkene **17** (95 mg, 0.22 mmol) in CH_2Cl_2 (2 mL). The mixture was warmed to room temperature. After 16 h, the mixture was diluted with ethyl acetate (20 mL) and washed with 1 M NaOH (3×10 mL) and brine (10 mL). The aqueous layer was back extracted with ethyl acetate (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to give a crystalline white solid. Chromatography on silica gel (1:2 petroleum ether/diethyl ether) provided the desired epoxide **18** (77 mg, 78 %) followed by the diastereomeric epoxide (7 mg, 7 %). (Both epoxides can be recrystallized from diethyl ether/hexanes.) Data for **18**: m.p. 101 °C; (lit.: [3k] 92–93 °C); $[\alpha]_D^{23} = +71.7°$ ($c = 1.62$, $CHCl_3$), {lit.:[3k] $+71.0°$ ($c = 0.9$, $CHCl_3$)}; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.4-7.2$ (m, 15H), 4.93 (d, $J = 10.7$ Hz, 1H), 4.86 (ABq, $J = 13.1$ Hz, $\Delta\tilde{\nu} = 15.6$ Hz, 2H), 4.77 (ABq, $J = 11.2$ Hz, $\Delta\tilde{\nu} = 23.2$ Hz, 2H), 4.54 (d, $J = 10.9$ Hz, 1H), 3.96 (dt, $J = 11.0$, 3.8 Hz, 1H), 3.85 (m, 2H), 3.59 (dd, $J = 10.0$, 8.1 Hz, 1H), 3.47 (t, $J = 10.0$ Hz, 1H), 3.34 (d, $J = 3.4$ Hz, 1H), 3.17 (d, $J = 3.9$ Hz, 1H), 2.18 (m, 1H), 1.94 (dd, $J = 8.1$, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 138.5$, 138.0, 137.6, 128.5, 128.3, 128.1, 127.9, 127.8, 127.6, 84.9, 79.8, 75.5, 75.3, 73.1, 62.7, 55.9, 2.9, 43.9; IR (neat): $\tilde{\nu} = 3314$, 3030, 2891, 1454, 1359, 1064 cm^{-1}. These data are consistent with those reported in the literature.[21] Data for the diastereomeric epoxide: m.p. 135–137 °C; $[\alpha]_D^{23} = +75.7°$ ($c = 0.17$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.4-7.2$ (m, 15H), 4.94–4.78 (m, 5H), 4.58 (d, $J = 11.5$ Hz, 1H), 3.88 (dd, $J = 8.5$, 1.7 Hz, 1H), 3.8–3.6 (m, 3H), 3.40 (t, $J = 10.0$ Hz, 1H), 3.31 (m, 1H), 3.13 (d, $J = 3.9$ Hz, 1H), 2.13 (dt, $J = 4.1$, 10.0 Hz, 1H), 1.11 (t, $J = 4.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 138.6$, 138.3, 138.2, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 82.3, 79.8, 75.8, 75.0, 72.8, 61.7, 54.9, 54.4, 44.1; IR (neat): $\tilde{\nu} = 3356$, 2923, 1072 cm^{-1}.

(1*S*,2*R*,3*S*,4*R*,5*R*,6*R*)-5-Hydroxymethyl-7-oxa-bicyclo[4.1.0]heptane-2,3,4-triol: **(+)-Cyclophellitol (1)**: Benzyl ether cleavage was carried out according to the method of Ziegler and Wang.[3k] The epoxide **18** (50 mg, 0.11 mmol) was dissolved in methanol (3.3 mL) and palladium hydroxide on carbon (Pearlman's catalyst, 25 mg) was added. The flask was evacuated and purged with H_2 three times, and then the mixture was stirred under an atmosphere of H_2 (balloon). After 12 h, the hydrogen was removed and the solution was filtered through a plug of celite and rinsed with methanol (10 mL). The filtrate was concentrated in vacuo to give a colorless oil. Chromatography on silica gel (10:1 to 3:1 CH_2Cl_2/MeOH gradient) provided (+)-cyclophellitol (**1**, 18 mg, 91 %) as a white crystalline solid. M.p. 145 °C (lit.:[1, 3b] 149–151 °C); $[\alpha]_D^{23} = +102°$ ($c = 0.70$, H_2O), {lit.: $[\alpha]_D^{27} = +103°$ ($c = 0.5$, H_2O),[3k] $[\alpha]_D^{24} = +103°$ ($c = 0.40$, H_2O),[3b] $[\alpha]_D^{20} = +97°$ ($c = 0.35$, H_2O)[3k]}; ^{1}H NMR (CD_3OD, 300 MHz): $\delta = 4.00$ (dd, $J = 10.7$, 4.4 Hz, 1H), 3.67 (m, 2H), 3.41 (m, 1H), 3.20 (dd, $J = 10.5$, 8.3 Hz, 1H), 3.06 (m, 2H), 1.97 (m, 1H); ^{13}C NMR (CD_3OD, 75 MHz): $\delta = 78.5$, 72.8, 68.8, 62.4, 57.4, 56.0, 45.9; IR (neat): $\tilde{\nu} = 3360$, 2895, 1641, 1081 $^{-1}$. These data are consistent with those reported in the literature.[1, 3k]

(3*R*)-(1′-Benzenesulfonyl-1′-nitromethyl)-(4*R*,5*S*,6*S*)-tris-(2,2,2-trichloroethoxycarbonyloxy)-cyclohexene (23): A slurry of the tetracarbonate **21** (4.0 g, 4.72 mmol), the sodium salt of phenylsulfonyl nitromethane **22** (1.13 g, 5.08 mmol), $[dba_3Pd_3]\cdot CHCl_3$ (120 mg, 0.115 mmol) and ligand (*R*,*R*)-**9** (240 mg, 0.348 mmol), Cs_2CO_3 in Eq. (2) in THF (13 mL) was stirred for 2.5 h. The reaction was concentrated in vacuo and column chromatography on silica gel (20–50 % EtOAc/petroleum ether) gave a mixture of diastereomers of **23** as a white solid (3.29 mg, 79 %). M.p. 103–105 °C (EtOAc/petroleum ether); ^{1}H NMR (300 MHz, $CDCl_3$): mixture of diastereomers $\delta = 8.0-7.4$ (m, 5H), 6.45 (d, $J = 10.5$, 0.5 Hz), 6.33 (d, $J = 10.5$, 0.5 Hz), 6.1–5.8 (m, 1.5H), 5.7–5.5 (m, 2H), 5.42 (m, 1H), 5.25 (t, $J = 9.8$, 0.5H), 5.0–4.6 (m, 6H), 4.0–3.8 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): mixture of diastereomers $\delta = 153.5$, 153.2, 136.5, 135.9, 135.6, 135.5, 129.9, 129.6, 129.3, 127.3, 126.1, 124.7, 124.0, 97.2, 94.0, 76.2, 75.4, 75.3, 74.5, 73.2, 43.8, 41.3; IR (neat): $\tilde{\nu} = 2965$, 1770, 1567, 1450, 1385, 1347, 1238 cm^{-1}; elemental analysis calcd (%) for $C_{22}H_{18}Cl_9NO_{13}S$: C 30.89, H 2.12, N 1.64; found: C 30.63, H 2.33, N 1.74.

(1*R*,4*R*,5*S*,6*S*)-4,5,6-Tris-(2,2,2-trichloro-ethoxycarbonyloxy)-cyclohex-2-enecarboxylic acid (25): Tetramethylguanidine (0.11 mL, 0.702 mmol) was added at 0 °C to a solution of nitrosulfone **23** (500 mg, 0.585 mmol) in

methylene chloride (2 mL) and the resulting solution was stirred for 10 min at 0 °C. Dimethyldioxirane (≈0.07–0.1M soln. in acetone) was added in 7 mL portions (21 mL total) until the reaction was complete by TLC analysis. The reaction mixture was concentrated and filtered through a plug of silica gel to give **25** as a white foam (318 mg, 78 %). $[\alpha]_D^{25} = -74.9°$ ($c = 1.75$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.97$ (m, 1H), 5.87 (m, 1H), 5.56 (m, 2H), 5.36 (m, 1H), 4.77 (m, 6H), 3.70 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 177.1$, 173.9, 153.2, 153.0, 125.9, 125.2, 94.1, 94.0, 76.2, 75.6, 72.8, 60.5, 47.3, 20.7; IR (neat): $\tilde{\nu} = 3320$, 2962, 1776, 1718, 1381, 1289, 1240 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{13}Cl_9O_{11}$: C 27.44, H 1.87; found: C 27.58, H 1.79.

(1*R*,2*S*,3*R*,4*S*,5*S*,6*S*)-5-Hydroxymethyl-2,3,4-tris-(2,2,2-trichloro-ethoxycarbonyloxy)-7-oxa-bicyclo[4.1.0]heptane (28) and **(1*S*,2*S*,3*R*,4*S*,5*S*,6*R*)-5-Hydroxymethyl-2,3,4-tris-(2,2,2-trichloro-ethoxycarbonyloxy)-7-oxa-bicyclo[4.1.0]heptane (29)**: 30 % Aqueous hydrogen peroxide (0.02 mL) was added to a solution of **26** (93.5 mg, 0.136 mmol) and methyltrioxorhenium (3.2 mg, 0.0129 mmol) in dichloroethane (0.15 mL). The resulting yellow solution was stirred for 40 h at room temperature. The reaction was diluted with methylene chloride (15 mL) and was washed with water (5 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give a colorless oil (crude 3.5:1 mixture of **28**:**29** by NMR analysis). Column chromatography on silica gel (33 % EtOAc/petroleum ether) gave **28** as a white foam (62 mg, 65 %). $[\alpha]_D^{25} = -36.3°$ ($c = 2.2$, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.24$ (td, $J = 8.3$, 1.7 Hz, 1H), 5.15 (d, $J = 8.1$ Hz, 1H), 5.02 (t, $J = 10.0$ Hz, 1H), 4.80 (m, 6H), 3.91 (m, 2H), 3.57 (br s, 1H), 3.30 (m, 1H), 2.49 (t, $J = 4.7$ Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 153.8$, 153.4, 153.0, 94.1, 93.5, 77.1, 76.7, 75.2, 71.7, 60.8, 55.4, 52.0, 42.0; IR (neat): $\tilde{\nu} = 3540$, 2961, 1771, 1378, 1290, 1239 cm^{-1}; elemental analysis calcd (%) for $C_{16}H_{13}Cl_9O_{11}$: C 27.36, H 2.15; found: C 27.54, H 2.34. Further chromatography gave a 7:1 mixture of **29**:**28** as a white foam (14 mg, 15 %). Spectral data for **29**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.33$ (m, 2H), 5.11 (m, 1H), 4.79 (m, 6H), 3.92 (d, $J = 11.5$ Hz, 1H), 3.81 (dd, $J = 3.2$, 11.5 Hz, 1H), 3.64 (d, $J = 3.9$ Hz, 1H), 3.36 (d, $J = 3.9$ Hz, 1H), 2.49 (dd, $J = 2.9$, 9.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 154.3$, 153.4, 153.1, 94.1, 77.1, 74.5, 73.3, 60.3, 54.3, 53.5, 42.9; IR (neat): $\tilde{\nu} = 3530$, 2962, 1772, 1376, 1289, 1240 cm^{-1}.

(1*R*,2*S*,3*R*,4*S*,5*S*,6*S*)-5-Hydroxymethyl-7-oxa-bicyclo[4.1.0]heptane-2,3,4-triol: **(−)-Cyclophellitol (1)**: K_2CO_3 (3 mg, 0.02 mmol) was added to a solution of **28** (42 mg, 0.060 mmol) in methanol (0.3 mL). The reaction was stirred at room temperature for 3 h and concentrated in vacuo. The crude residue was diluted with methylene chloride (0.5 mL), and filtered through silica gel (20 % methanol/methylene choride) to give (−)-**1** as a white solid (10.1 mg, 95 %). $[\alpha]_D^{25} = -89.8°$ ($c = 0.5$, H_2O). After recrystallization from water: m.p. 142–144 °C; $[\alpha]_D^{23} = -100.7°$ ($c = 0.32$, H_2O); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.90$ (dd, $J = 10.4$, 4.2 Hz, 1H), 3.54 (m, 2H), 3.30 (d, $J = 3.5$ Hz, 1H), 3.09 (m, 1H), 2.94 (m, 2H), 1.85 (tdd, $J = 9.5$, 4.6, 1.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 78.5$, 72.8, 68.8, 62.5, 57.4, 56.0, 45.9; IR (neat): $\tilde{\nu} = 3362$, 2921, 1642, 1426 cm^{-1}; HRMS: calcd for $C_7H_{11}O_4$ $[M - OH]^+$: 159.0657; found: 159.0665.

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