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Synthetic studies of pestalotiopsin A: asymmetric synthesis of the 2-oxabicyclo[3.2.0]heptane substructure

Ken-ichi Takao, Hiroshi Saegusa, Tomohiro Tsujita, Takenori Washizawa and Kin-ichi Tadano*

Department of Applied Chemistry, Keio University, Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

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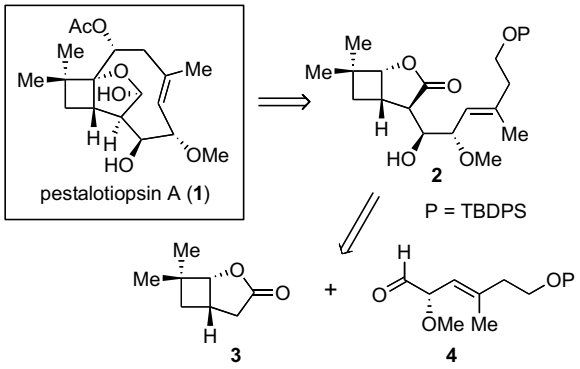
Abstract—A functionalized 2-oxabicyclo[3.2.0]heptan-3-one derivative, possessing all the skeletal carbons of pestalotiopsin A, has been synthesized. For the preparation of intermediary cyclobutane derivatives in enantioenriched form, the Lewis acid-catalyzed [2+2] cycloaddition of *N*-propiolated Oppolzer's camphorsultam with dimethylketene bis(trimethylsilyl) acetal followed by a stereoselective 1,4-hydride addition/protonation, has been developed.

Through investigation of the metabolites produced by *Pestalotiopsis* sp., an endophytic fungus associated with the bark and leaves of the Pacific yew tree (*Taxus brevifolia*), some new caryophyllene-type sesquiterpenoids were isolated.[1] Among them, pestalotiopsin A (**1**, Scheme 1) showed immunosuppressive activity in the mixed lymphocyte reaction. Its relative structure was determined by extensive spectroscopic analysis and confirmed by single-crystal X-ray diffraction, although its absolute stereochemistry remained unclear. Compound **1** has an unprecedented oxatricyclic structure consisting of a geminally methylated cyclobutane ring fused with a highly oxygenated (*E*)-cyclononene ring and a γ-lactol. Its novel molecular architecture and interesting biological activity have made compound **1** an attractive synthetic target. Procter and co-workers have established a route to the 2-oxabicyclo[3.2.0]heptane core of **1** by using the samarium(II)-mediated 4-*exo*-*trig* ketyl-olefin cyclizations.[2] Paquette and co-workers have explored the zirconocene-mediated ring contraction for the preparation of multi-substituted cyclobutane derivatives, aiming at the synthesis of cyclobutane-containing natural products represented by **1**.[3] Herein, we describe our efforts toward the synthesis of **1** based on an asymmetric [2+2] cycloaddition approach to highly functionalized cyclobutane derivatives.



Scheme 1. Structure of pestalotiopsin A (**1**) and retrosynthetic analysis.

As the absolute stereochemistry of pestalotiopsin A was undetermined, we arbitrarily targeted the enantiomer **1** depicted in Scheme 1. A 2-oxabicyclo[3.2.0]heptan-3-one derivative **2**, possessing all the skeletal carbons of **1**, was considered to be an advanced synthetic intermediate. The installation of the side chain in **2** would be achieved by the aldol reaction of bicyclic lactone **3** with a β,γ-unsaturated hexenal derivative **4**. The former **3** was envisioned to be prepared from a multi-substituted cyclobutane in enantiomerically enriched form. The

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* Corresponding author. Tel./fax: +81 45 566 1571; e-mail: tadano@applc.keio.ac.jp

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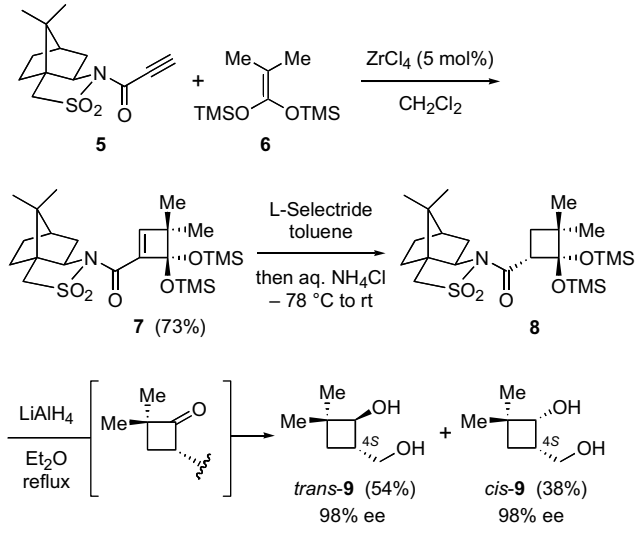
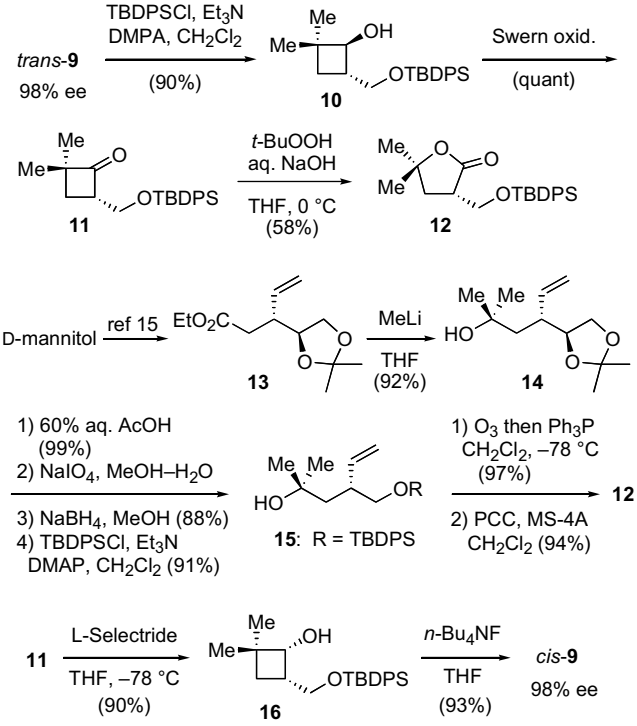
preparation of optically active cyclobutane compounds as well as their applications to natural products synthesis is one of the most attractive topics in current organic synthesis.[4,5]

It has been reported that some propiolic acid esters feasibly undergo [2+2] cycloaddition with ketene silyl acetals to provide cyclobutene derivatives, which were reduced to cyclobutane derivatives.[6] Asymmetric induction in these reaction sequences was expected to be realized by using a chiral auxiliary strategy. Therefore, Oppolzer's (1*S*)-camphorsultam **5**, incorporating an *N*-propioloyl group, was prepared according to the procedure described in the literature[7] (Scheme 2). The [2+2] cycloaddition of **5** with dimethylketene bis(trimethylsilyl) acetal (**6**)[8] proceeded under Rousseau's conditions[6a] (in the presence of a catalytic amount of $ZrCl_4$ in CH_2Cl_2), giving a single regioisomeric adduct **7**.[9] The 1,4-hydride addition/protonation of cyclobutenecarbonyl amide **7** by using lithium tri-*s*-butylborohydride (L-Selectride) in toluene[10] realized an excellent level of stereoinduction to provide cyclobutane **8** in an almost diastereomerically single form. Removal of the chiral auxiliary in **8** with lithium aluminum hydride induced the simultaneous cleavage of the silyl acetal and the subsequent reduction of the resulting cyclobutanone. As a result, two diastereomers of cyclobutanols, *trans*-**9** and *cis*-**9**,[11,12] were obtained with 98% ee.[13] Oppolzer's camphorsultam was quantitatively recovered.

The absolute configurations at C4 in the enantioenriched (98% ee) *trans*-**9** and *cis*-**9** were assigned to be (*S*) by chemical transformation as shown in Scheme 3. Selective protection of the primary hydroxy group in *trans*-**9** provided mono-silyl ether **10**, which was oxidized to cyclobutanone **11**. The Baeyer–Villiger reaction of **11** proceeded regioselectively to produce γ-lactone **12**.[14] On the other hand, the known D-mannitol-derived ester **13**,[15] whose absolute stereochemistry had been unambiguously determined, was treated with an excess of methyllithium to provide tertiary alcohol **14**. Conversion of **14** into 4-methyl-1,4-butanediol derivative **15** was achieved through four standard transformations. Ozonolysis of the vinyl group in **15**, followed by a reductive workup, resulted in the formation of γ-lactol. The oxidation of the γ-lactol provided the γ-lactone **12**, whose retention time on chiral HPLC analysis matched well with that of the aforementioned major enantiomer **12** derived from *trans*-**9**. Furthermore, a comparison of the specific rotation of these samples established the absolute stereochemistry of C4 in *trans*-**9** as an *S*-configuration. Because both *trans*-**9** and *cis*-**9** were derived from the almost diastereomerically pure **8**, these cyclobutanols were considered to have an identical configuration at C4, which was experimentally evidenced as follows. The cyclobutanone **11**, obtained from *trans*-**9**, was reduced with L-Selectride to provide **16** as a single diastereomer. By desilylation of **16**, *cis*-**9** was obtained without a loss of optical purity (determined by chiral HPLC analysis).

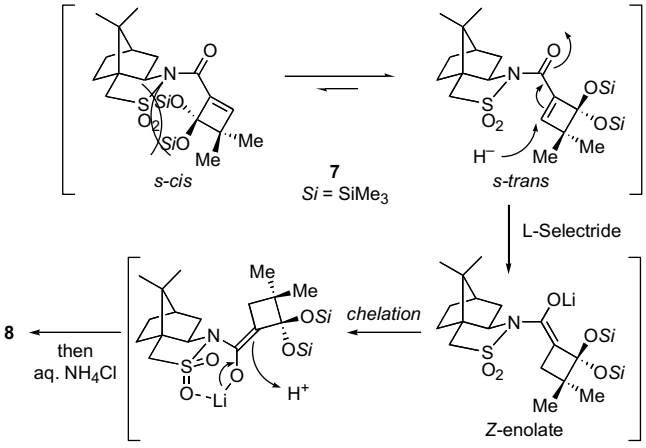


Scheme 2. Asymmetric synthesis of cyclobutanols, *trans*-**9** and *cis*-**9**.



Scheme 3. Determination of absolute stereochemistries at C4 in *trans*-**9** and *cis*-**9**.

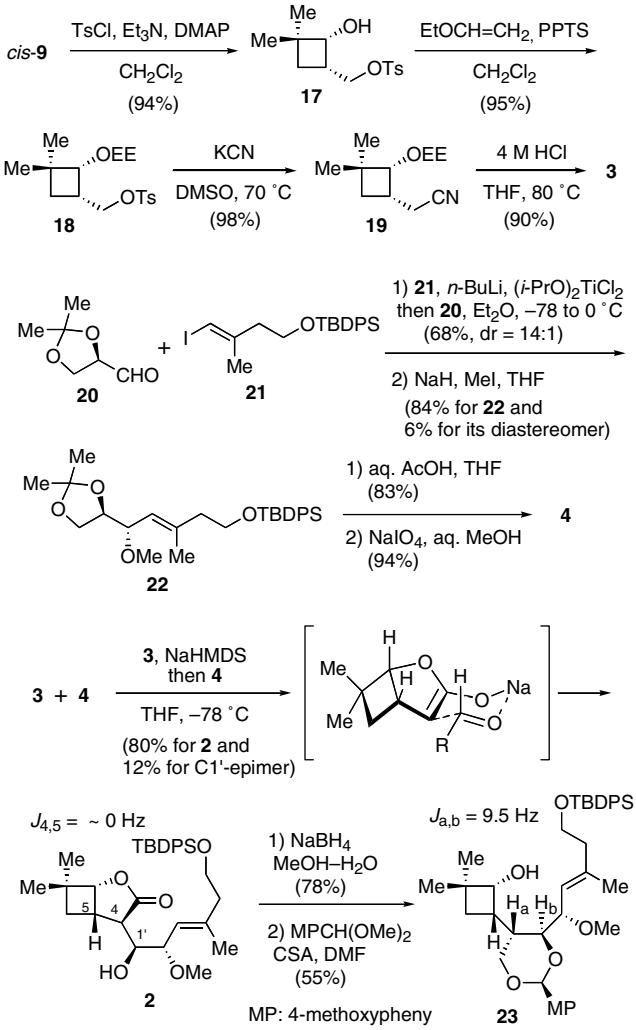
The observed high level of stereoselection in the tandem 1,4-hydride addition/protonation in the case of **7** can be rationalized using the well-recognized transition-state argument depicted in Scheme 4.[16] In the more favorable conformation of **7**, the carbonyl group directs *anti* to the SO_2 group and changes to *s*-*trans* conformation to the α,β-unsaturated bond as depicted to avoid a steric repulsion occurring between bis(trimethylsilyloxy) and the SO_2 groups in the *s*-*cis* conformer. Then, the 1,4-hydride addition to the *s*-*trans* conformer generates the *Z*-enolate intermediate, which is reorganized to the lithium-chelated conformer as depicted. A proton approaches from the side opposite the bulky auxiliary (from the front side). As a result, **8** was obtained almost exclu-



Scheme 4. Plausible mechanism for 1,4-hydride addition/protonation of **7**.

sively. In contrast, the use of Evans' 4-benzyloxazolidinone as the chiral auxiliary for the two-step reduction gave a lower level of asymmetric induction (13% ee).[17]

Having established the method for asymmetric synthesis of the multi-substituted cyclobutanes *trans*-**9** and *cis*-**9**, we turned our attention to the construction of the advanced synthetic intermediate **2** via **3** (Scheme 5). For the synthesis of the *cis*-fused bicyclic lactone **3**, *trans*-**9** was converted into *cis*-**9** by the procedure described in Scheme 3. Selective tosylation of *cis*-**9** and protection of the secondary hydroxy group in the resulting **17** gave the ethoxyethyl (EE) ether **18**. The tosyl group in **18** was replaced by a cyano group to provide **19**.[18] Exposure of **19** to 4 M hydrochloric acid/THF hydrolyzed the ethoxyethyl ether to regenerate the secondary alcohol, which underwent spontaneous cyclization under the conditions. The resulting bicyclic lactone **3**[19] was the substrate for the aimed aldol reaction. The coupling partner of the aldol reaction, the chiral aldehyde **4**, was synthesized from D-glyceraldehyde acetonide **20**. The addition of the vinyllithium derivative, prepared from the known vinyl iodide **21**,[20] to **20** in the presence of $(i\text{-PrO})_2TiCl_2$[21] proceeded *anti*-selectively (dr = 14:1). In the absence of $(i\text{-PrO})_2TiCl_2$, the reaction of **20** and **21** showed lower diastereoselectivity (3:1). Subsequent methylation of the resulting adduct afforded diastereomerically pure methyl ether **22** after chromatographic separation of the minor isomer.[22] Deprotection of the isopropylidene group in **22**, followed by oxidative cleavage of the resulting diol, provided the hexenal derivative **4**.[23] The aldol reaction of **3** with **4** was achieved stereoselectively by using sodium bis(trimethylsilyl)amide as a base.[24] This provided the desired *anti*-aldol **2**[25] predominately. In both ^1H NMR spectra of **2** and the minor adduct, the lack of a coupling constant between H4 and H5 (nearly 0 Hz) was observed. Thus, the dihedral angle between the two protons was almost 90°, and the stereochemistry of C4 for both adducts was determined as depicted. To confirm the stereochemistry of C1′ (C1 of the side chain at C4), we carried out the transformation of **2** into *p*-methoxybenzylidene acetal **23**, of which the ^1H NMR spectrum showed diaxial coupling ($J = 9.5$ Hz) between H_a and H_b. Consequently,



Scheme 5. Synthesis of 2-oxabicylo[3.2.0]heptan-3-one derivative **2**.

the stereochemistry of **2** was determined as depicted. In this aldol reaction, high stereocontrols at C4 and C1′ were observed. It was assumed that the aldehyde **4** approached from the convex face of the bicyclo[3.2.0]-heptane skeleton and the reaction proceeded predominantly via the sodium enolate-chelated chair-like transition state as depicted, leading to *anti*-aldol adduct **2**.

In conclusion, we have developed an asymmetric synthesis of the multi-substituted cyclobutane derivatives *trans*-**9** and *cis*-**9**, featuring the [2+2] cycloaddition of *N*-propioloyl sultam **5** and ketene bis(trialkylsilyl) acetal **6**. This strategy was successfully applied to the synthesis of the advanced synthetic intermediate **2**,[26] including all the skeletal carbons of pestalotiopsin A (**1**). Further studies toward the total synthesis of **1** are in progress in this laboratory.

Acknowledgments

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12. Among two diastereomers *trans*-**9** and *cis*-**9**, the less polar compound was able to be converted into the bicyclic lactone **3** (see Scheme 5). Accordingly, the less polar isomer was determined to be *cis*-**9**.
13. Compound *trans*-**9** was obtained as a colorless oil: TLC R_f 0.38 (acetone–toluene, 1:1); $[\alpha]_D^{22}$ −10.3 (*c* 0.540, $CHCl_3$); IR 3350, 2960 cm^{-1}; ^{1}H NMR δ 1.06 (t, 1H, $J = 10.1$ Hz), 1.07 (s, 3H), 1.19 (s, 3H), 1.59 (t, 1H, $J = 10.1$ Hz), 2.29 (m, 1H), 2.44–2.60 (br, 2H, OH), 3.62 (dd, 1H, $J = 7.5$, 10.8 Hz), 3.63 (d, 1H, $J = 8.4$ Hz), 3.71 (dd, 1H, $J = 5.3$, 10.8 Hz); ^{13}C NMR δ 20.9, 28.2, 30.0, 38.3, 43.2, 65.4, 77.1; HRMS calcd for $C_7H_{13}O_2$ (M^+−H) *m*/*z* 129.0916, found 129.0913; HPLC analysis (column, Daicel Chiralcel OD-H, EtOH–hexane = 1:40, flow rate = 0.7 mL/min); t_R(min) = 36.3 for the mono-tosylate of (1*S*,4*S*)-isomer, 38.9 for the mono-tosylate of (1*R*,4*R*)-isomer. Compound *trans*-**9** was determined to be 98% ee. Compound *cis*-**9** was obtained as a colorless oil: TLC R_f 0.56 (acetone–toluene, 1:1); $[\alpha]_D^{24}$ +29.0 (*c* 1.27, $CHCl_3$); IR 3360, 2950 cm^{-1}; ^{1}H NMR δ 1.08 (s, 3H), 1.12 (s, 3H), 1.60 (dd, 1H, $J = 7.7$, 11.2 Hz), 1.65 (ddd, 1H, $J = 1.5$, 8.6, 11.2 Hz), 2.09–2.23 (br, 2H, OH), 2.66 (m, 1H), 3.78 (dd, 1H, $J = 4.6$, 11.2 Hz), 3.88 (dd, 1H, $J = 8.3$, 11.2 Hz), 4.09 (dd, 1H, $J = 1.5$, 7.5 Hz); ^{13}C NMR δ 22.3, 28.8, 32.2, 35.4, 37.9, 63.3, 76.5; HRMS calcd for $C_7H_{13}O_2$ (M^+−H) *m*/*z* 129.0916, found 129.0916; HPLC analysis (column, Daicel Chiralcel OD-H, EtOH–hexane = 1:20, flow rate = 0.7 mL/min); t_R(min) = 15.3 for the mono-tosylate of (1*R*,4*S*)-isomer, 17.1 for the mono-tosylate of (1*S*,4*R*)-isomer. Compound *cis*-**9** was determined to be 98% ee.
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17. It is likely that a steric repulsion occurring between the benzyl group in the Evans' auxiliary and the bis(OTMS) groups makes its *s-trans* conformation unfavorable.
18. When the unprotected tosylate **17** was treated with KCN in hot dimethyl sulfoxide, a ring-opening reaction involving elimination of the tosyl group occurred, forming an acyclic product.
19. Compound **3** was obtained as a colorless oil: TLC R_f 0.53 (EtOAc–hexane, 1:2); $[\alpha]_D^{24}$ −119 (*c* 1.41, $CHCl_3$); IR 2960, 1780 cm^{-1}; ^{1}H NMR δ 1.05 (s, 3H), 1.21 (s, 3H), 1.58 (dd, 1H, $J = 7.0$, 12.1 Hz), 2.06 (dddd, 1H, $J = 0.7$, 2.6, 9.0, 12.1 Hz), 2.39 (dd, 1H, $J = 1.8$, 18.3 Hz), 2.65 (ddd, 1H, $J = 0.7$, 9.2, 18.3 Hz), 3.07 (m, 1H), 4.50 (dd, 1H, $J = 2.6$, 5.9 Hz); ^{13}C NMR δ 22.4, 26.8, 28.2, 35.1, 38.8, 38.8, 86.3, 178.6; HRMS calcd for $C_8H_{12}O_2$ (M^+) *m*/*z* 140.0837, found 140.0838.
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22. The stereochemistry of the newly introduced stereogenic center in **22** was determined by chemical transformation.
23. Compound **4** was obtained as a colorless oil: TLC R_f 0.65 (EtOAc–hexane, 1:2); $[\alpha]_D^{24}$ +83.4 (*c* 1.23, $CHCl_3$); IR 2940, 1730 cm^{-1}; ^{1}H NMR δ 1.03 (s, 9H), 1.74 (d, 3H, $J = 1.0$ Hz), 2.32 (t, 2H, $J = 6.5$ Hz), 3.37 (s, 3H), 3.76 (t, 2H, $J = 6.5$ Hz), 4.39 (dd, 1H, $J = 1.5$, 8.6 Hz), 5.08 (dq, 1H, $J = 8.6$, 1.0 Hz), 7.35–7.47 (m, 6H), 7.62–7.66 (m, 4H), 9.46 (d, 1H, $J = 1.5$ Hz); ^{13}C NMR δ 17.6, 19.1, 26.8 × 3, 42.7, 56.7, 62.2, 83.4, 118.7, 127.7 × 4, 129.6 × 2, 133.7 × 2, 135.5 × 4, 143.0, 198.6; HRMS calcd for $C_{20}H_{23}O_3Si$ (M^+−*t*-C_4H_9) *m*/*z* 339.1417, found 339.1415.
24. With LDA as a base, the combined yield of the aldol adducts diminished to 36% (**2**–epimer = 2.3:1).
25. Compound **2** was obtained as a colorless oil: TLC R_f 0.45 (EtOAc–hexane, 1:3); $[\alpha]_D^{23}$ −59.0 (*c* 1.08, $CHCl_3$); IR 3490, 2930, 1770 cm^{-1}; ^{1}H NMR δ 0.98 (s, 3H), 1.03 (s, 9H), 1.16 (s, 3H), 1.40 (dd, 1H, $J = 7.3$, 12.1 Hz), 1.88 (d, 3H, $J = 1.0$ Hz), 1.90 (ddd, 1H, $J = 2.9$, 8.4, 12.1 Hz), 2.32 (t, 2H, $J = 6.3$ Hz), 2.41 (br s, 1H), 2.91 (m, 1H), 3.06 (br, 1H, OH), 3.25 (s, 3H), 3.56 (dd, 1H, $J = 1.8$, 9.2 Hz), 3.75–3.80 (m, 2H), 4.29 (t, 1H, $J = 9.2$ Hz), 4.46 (dd, 1H, $J = 2.9$, 5.5 Hz), 4.94 (m, 1H), 7.35–7.47 (m, 6H), 7.62–7.67 (m, 4H); ^{13}C NMR δ 17.3, 19.1, 22.4, 26.5, 26.8 × 3, 34.9, 38.3, 38.6, 42.9, 48.8, 55.7, 62.2, 76.1, 77.7, 86.4, 122.2, 127.7 × 4, 129.6 × 2, 133.8 × 2, 135.5 × 4, 142.6, 178.2; HRMS calcd for $C_{28}H_{35}O_5Si$ (M^+−*t*-C_4H_9) *m*/*z* 479.2254, found 479.2256.
26. The enantiomer of **2** would be synthesized from (1*R*)-camphorsultam (in place of the 1*S*-isomer) and L-glyceraldehyde acetonide (in place of **20**) in the same reaction sequence.