Natural Products

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Annulation Approach to Doubly Linked (A-type) Oligocatechins: Syntheses of (+)-Procyanidin A_2 and (+)-Cinnamtannin B_1**

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In memory of Karsten Krohn

Abstract: *The first stereoselective syntheses of doubly linked (A-type) oligocatechins, (+)-procyanidin A_2 and (+)-cinnamtannin B_1, have been achieved. Ethylenedioxy-bridged flavans served as excellent platforms, thus allowing annulation with nucleophilic catechin units in a stereoselective manner. An additional key was the new synthetic approach to selectively protected nucleophilic catechin, thus enabling regioselective construction of the key dioxabicyclo skeleton of the A-type oligocatechins.*

The A-type procyanidins,[1] such as **1** and **2**, are unique among the oligomeric catechins,[2] which are characterized by the unusual bridged structure of a dioxabicyclo[3.3.1]nonane composed of two catechin skeleta (Figure 1). Recently,

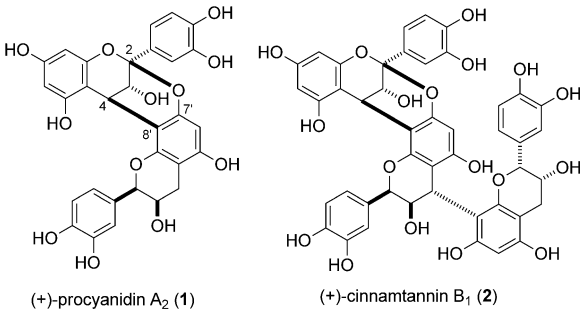
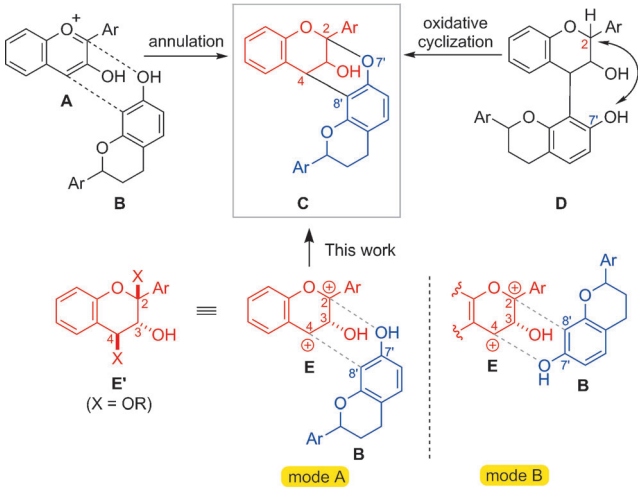


Figure 1. Doubly linked (A-type) oligocatechins.

potential bioactivities of such compounds have been unveiled, including the sweetness of (+)-cinnamtannin B_1 (**2**),[3] which also exhibits an insulin-enhancing activity relevant to diabetes treatment.[4] However, further studies on the structure–activity relationship of such a unique class of catechin oligomers have been limited by the scarcity of natural products, thus calling for the development of organic synthesis route.



Scheme 1. Two proposed biosynthetic paths and our synthetic strategy.

In planning for their synthesis, the key challenge of the construction of the dioxabicyclo skeleton and the putative biogenesis of the double interflavan linkage is worth considering (Scheme 1). Among two proposed possibilities, one is the annulation via the flavylium ion **A** with the nucleophilic catechin unit **B** to form **C**, which was exploited in the biomimetic synthetic study by Jurd et al.[5] Although this process allows the dual bond formation, a limitation is the planar nature of **A**, rendering enantiocontrol difficult. Another possible biogenesis is the oxidative cyclization of the type-B dimer **D**. Although this cyclization has not been exploited for synthetic purposes, it provides insight into the origin of the enhanced antioxidant activity of dimers in comparison with the monomers.[6]

These proposals have inspired us to exploit the formal dicationic species **E** (Scheme 1). The requisite dioxabicyclo skeleton could be accessed quickly if the following two requirements were fulfilled: 1) design of a suitable precursor for the generation of **E**, and 2) regioselective two-bond formations shown as mode A, not vice versa (mode B). If viable, an additional hope was that the C3 stereocenter in **E** would provide stereochemical control.

Reported herein is the successful implementation of this strategy, culminating in the first stereoselective total syntheses of (+)-procyanidin A_2 (**1**) and (+)-cinnamtannin B_1 (**2**).

The first task was to design the synthetic equivalent, **E′**, of the dication **E** (Scheme 1). Assuming that the leaving groups (X) at C2 and C4 in **E′** could be alkoxy groups, it would be available by a prior change in the oxidation level of the

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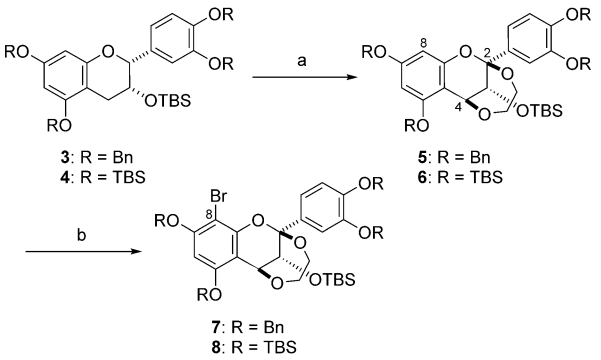
catechin derivatives. Initial attempts were made to oxidize the epicatechin derivative **3**[7] with DDQ in the presence of various alcohols, however, primarily the 4-alkoxy product and trace amounts of the 2-alkoxy and 2,4-dialkoxy products were obtained (see Scheme 2).[8] After considerable experimentation, an excellent result was obtained by the use of ethylene glycol as the alkoxy source: heating of **3** with DDQ (4.0 equiv) in the presence of ethylene glycol (1.5 equiv, CH_2Cl_2, reflux, 8 h) gave 69% yield of **5** with a 2,4-ethylenedioxy bridge (Scheme 2). A diagnostic ^{13}C NMR signal

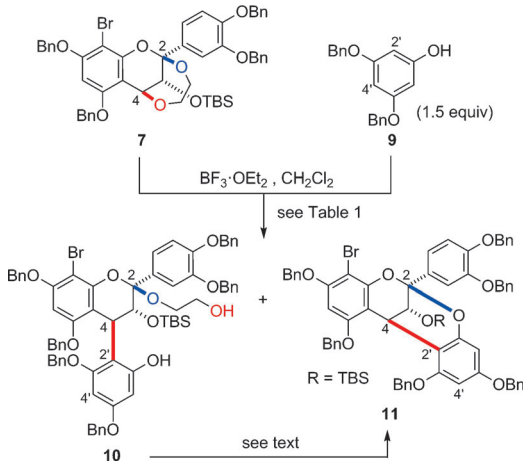


Scheme 2. 2,4-Dialkoxylation and C8 capping. Reaction conditions and reagents: a) DDQ (4 equiv), $(CH_2OH)_2$ (1.5 equiv), CH_2Cl_2, reflux, 8 h (69% for **5**, 81% for **6**). b) *N*-bromosuccinimide (1.1 equiv), CH_2Cl_2, −10 °C, 1 h (97% for **7** and 95% for **8**). DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, TBS = *tert*-butyldimethylsilyl.

was observed at $\delta = 101.5$ ppm ($CDCl_3$), which is assigned to the C2-acetal center. Under these reaction conditions, the per-silyl surrogate **4**[9] was also converted into the corresponding dioxy product **6** in 81% yield.[10] In preparation for the next stage, the C8-positions of **5** and **6** were masked by a bromine atom, giving the bromides **7** and **8**, respectively, in excellent yields. The purpose of this bromo-capping was to suppress self-reactions of these dication catechin precursors under the planned Lewis-acidic activation conditions.[11]

With these dication precursors in hand, a preliminary study on the annulation reaction was carried out by using **7** and di-*O*-benzyl phloroglucinol (**9**) as the model reaction partners (Scheme 3). A mixture of **7** and **9** in CH_2Cl_2 was treated with $BF_3{\cdot}OEt_2$ at −78 °C. During the gradual warming to −40 °C over 2 hours, the starting material **7** was almost consumed, and two new products were produced (Table 1, entry 1). The major product (66% yield) was the singly linked **10** with a C4–C2′ bond, and the structure was verified by extensive NMR correlations. Pleasingly, the minor product (20% yield) was **11**, having the desired dioxabicyclic structure, which was assigned by NOE studies and the diagnostic ^{13}C-acetal signal at $\delta = 100.5$ ppm.[12] Importantly, **10** and **11** were the respective single stereoisomers as shown.

The singly linked **10** is the precursor to **11**: upon re-exposure to the same reaction conditions, **10** was converted into **11**. Thus, the annulation was proven to proceed in a stepwise manner, thus starting with the formation of the C4–C2′ bond from the β side to give **10** followed by the C2–O bond formation. Eventually we found the annulation of **7** and



Scheme 3. Model study for annulation reaction.

Table 1: Reaction conditions and results for annulation reaction.

Entry	*t* [h][a]	*T* [°C]	Product (Yield [%][b])
1	2	−78→−40	**10** (66), **11** (20)
2	3	−78→−20	**11** (93)

[a] Duration of gradual warming. [b] Yield of isolated product.

9 could be completed by using a longer reaction time (3 h) and a higher temperature (−20 °C), giving **11** in 93% yield (Table 1, entry 2).[13]

The mechanistic rationale for the initial activation of **7** at C4 rather than at C2 could be the difference in the relative stability of their cations (Figure 2): the C2 cation would be

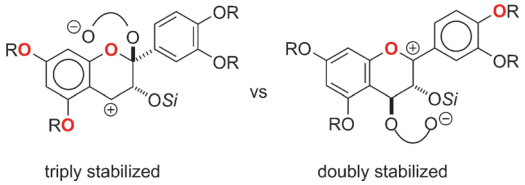
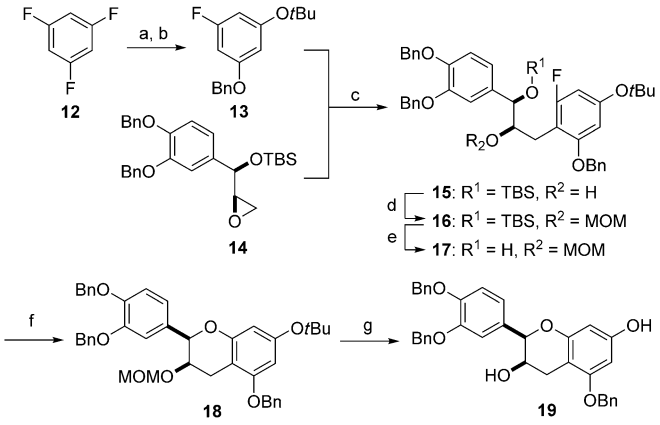


Figure 2. Benzyl cation stabilization by oxy functions.

stabilized by lone pairs on two oxygens, while the C4 cation would be triply stabilized. The resulting highly stabilized C4-cationic species could be trapped by **9**, which is sufficiently reactive at C2′.[14] The second activation generates the cation at C2, followed by its intramolecular capture by the phenolic oxygen atom to produce **11**.

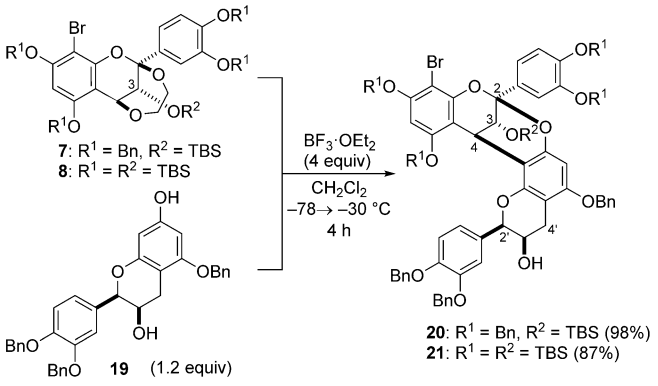
With these promising data for the key annulation, we proceeded with the total synthesis of the A-type oligocatechins. The first target was procyanidin A_2 (**1**), for which the selectively protected flavan unit **19** was prepared from 1,3,5-trifluorobenzene (**12**; Scheme 4).[15] Sequential treatment of **12** with potassium *tert*-butoxide and sodium benzyloxide gave the fluoride **13** in excellent yield. Regioselective lithiation of **13** (*n*BuLi, THF, −78 °C, 1 h)[16] and subsequent reaction with the epoxide **14** (>99% *ee*)[17] in the presence of $BF_3{\cdot}OEt_2$



Scheme 4. Reaction conditions and reagents: a) *t*BuOK (1.2 equiv), DMF, 2 h (93%). b) BnOH (1.3 equiv), NaH (1.5 equiv), DMF, 12 h (97%). c) *n*BuLi (1.95 equiv), THF, −78°C, 1 h; **14**, $BF_3{\cdot}OEt_2$ (1.9 equiv), −78°C, 30 min (95%). d) MOMCl (3 equiv), iPr_2NEt (5 equiv), nBu_4NI (10 mol%), 7 h. e) nBu_4NF (1.1 equiv), THF, 20 h (96%, 2 steps). f) KH (1.5 equiv), THF, 24 h (93%). g) PPTS (2 equiv), phloroglucinol (5 equiv), EtOH, reflux, 24 h (90%). DMF = *N*,*N*-dimethylformamide, MOM = methoxymethyl, PPTS = pyridinium *p*-toluenesulfonate, THF = tetrahydrofuran.

gave the adduct **15** in 95% yield. Protection of **15** as a MOM ether and subsequent removal of the silyl group gave the alcohol **17** (94% yield), which is ready for the pyran cyclization. Treatment of **17** with KH (THF, RT, 24 h)[18] cleanly gave the pyran **18** in excellent yield. The C2–C3 *cis* relationship in **18** was verified by ^1H NMR analysis ($J_{2,3} = < 0.5$ Hz). In the presence of phloroglucinol, as a scavenger of the electrophilic C1 species generated during the MOM deprotection,[15] treatment of **18** with PPTS in EtOH cleanly removed the MOM and *tert*-butyl groups, giving **19** in 90% yield.

With coupling partners **7** and **19** in hand, the key annulation was examined (Scheme 5). Pleasingly, upon treatment of a mixture of **7** and **19** with $BF_3{\cdot}OEt_2$ (CH_2Cl_2, −78→−30°C, 4 h), the desired annulation product **20** was cleanly formed in excellent yield. Formation of the C2-acetal center was ascertained by a diagnostic signal at $\delta = 100.8$ ppm ($CDCl_3$) in the ^{13}C NMR spectra. Under the same reaction



Scheme 5. Annulation of the 2,4-dialkoxylflavan unit **7** and **8** and nucleophilic unit **19**.

conditions, annulation of the silyl ether **8** and **19** also proceeded smoothly, giving the corresponding annulation product **21** in 87% yield. The rigorous stereo- and regioselectivities are notable. No other isomers were obtained in either case. As the α face of either the electrophilic flavan unit **7** or **8** was blocked by the C3 substituent, the nucleophile **19** approached from the opposite side (β-side) to form the double β linkages at the C2 and C4-positions. Recrystallization of **21** gave single crystals suitable for X-ray diffraction analysis (Figure 3).[19]

Scheme 6 shows the final stage of the synthesis by removal of all protecting groups. After removal of the silyl group in **20** (nBu_4NF, THF, RT, 8 h), all the benzyl groups and the bromine atom were simultaneously removed by hydrogenolysis [H_2 (1 atm), 5% $Pd(OH)_2/C$ (ASCA2),[20] MeOH/THF/H_2O (v/v/v = 4:4:1), 2.5 h]. Anaerobic filtration through a glass-fiber filter (argon) and partial concentration followed

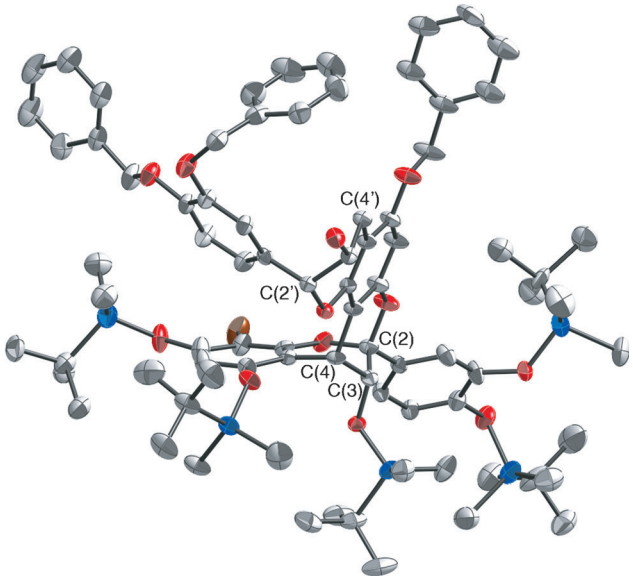
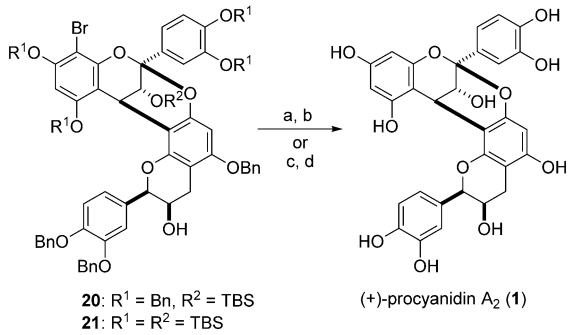


Figure 3. X-ray crystal structure of **21**. Hydrogen atoms and disordered atoms are omitted for clarity. Thermal ellipsoids set at 30% probability.

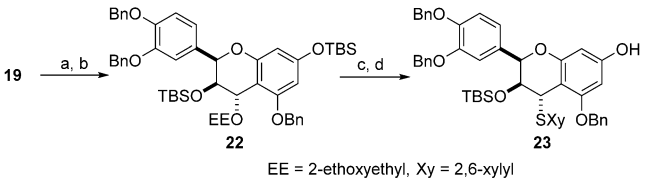


Scheme 6. Synthesis of (+)-procyanidin A_2 (**1**). Reaction conditions and reagents for the reaction of **20**: a) nBu_4NF (1.5 equiv), THF, 8 h (quant.). b) H_2, ASCA2 [5% $Pd(OH)_2/C$], 1 h (99%). Reaction conditions and reagents for the reaction of **21**: c) nBu_4NF (20 equiv), NH_4F (20 equiv), THF, reflux, 5 h (91%). d) H_2 (1 atm), ASCA2 [5% $Pd(OH)_2/C$], THF, MeOH, H_2O, 1 h (quant.).

by lyophilization[11] gave an almost-pure sample of **1** (as assessed by ^{1}H NMR spectroscopy). Further purification by reverse-phase column chromatography (Cosmosil 140C18-OPN, MeOH/H_2O = 15/85→40/60) and lyophilization gave pure (+)-procyanidin A_2 (**1**) as a snow-white solid (99% yield), which was identical with the authentic sample[21] as determined by direct comparison (^{1}H and ^{13}C NMR spectroscopy, IR, high-resolution ESI-MS, HPLC).[12] The optical rotation was $[\alpha]_D^{23}$ = +54 (c = 0.96, acetone) {lit.[1a] $[\alpha]_D$ = +55.63 (c = 1.08, acetone)}.

The silyl-protected compound **21** was also converted into **1**, but careful choice of the reaction conditions was necessary. The difficulty was that treatment of **21** with nBu$_4$NF (THF, room temperature) allowed rapid removal of the silyl groups attached to the phenols, but the one attached to the C3 alkanol remained intact. Prolonged reaction only led to decomposition, which is in line with the pronounced instability of catechins under basic conditions once the catechol moiety is liberated.[22] However, we found that a large excess of nBu$_4$NF, buffered by NH_4F,[23] allowed full removal of the silyl groups in **21** (THF, reflux, 5 h). Finally, hydrogenolysis removed the benzyl groups and the bromine atom, giving the final product **1** in excellent yield.

We then tackled the synthesis of a trimeric natural product, (+)-cinnamtannin B_1 (**2**), which is known as a rare sweet polyphenol.[1b,3] As the catechin unit for the second coupling, the sulfide **23**, which could be activated under soft Lewis-acidic conditions,[11] was prepared from **19** (Scheme 7).

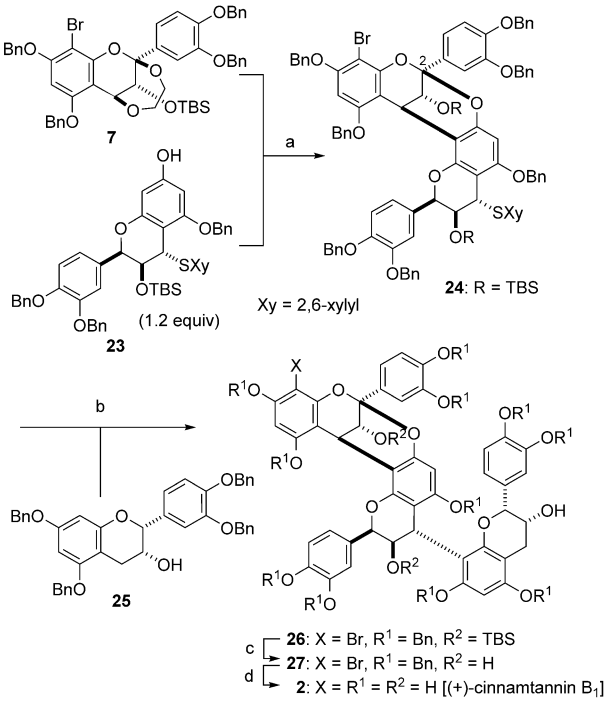


Scheme 7. Preparation of nucleophilic unit **23**. Reaction conditions and reagents: a) TBSCl (3 equiv), imidazole (10 equiv), DMF, RT, 24 h (97%). b) DDQ (1.5 equiv), 2-ethoxyethanol (5 equiv), CH_2Cl_2, RT, 1.5 h (61%). c) $BF_3{\cdot}OEt_2$ (1.5 equiv), HSXy (5 equiv), CH_2Cl_2, −78→−70 °C, 1.5 h (93%). d) nBu$_4$NF (1.5 equiv), AcOH (1.5 equiv), THF, 0 °C (97%). Xy = 2,6-xylyl.

After silylation of **19**, DDQ oxidation in the presence of 2-ethoxyethanol[24] gave the 4-alkoxy flavan **22**, which was converted into the sulfide **23** in 93% yield by treatment with 2,6-xylyl-1-thiol (HSXy) in the presence of $BF_3{\cdot}OEt_2$.

The annulation of **7** and **23** proceeded smoothly by using $BF_3{\cdot}OEt_2$ to give the annulation product **24** in 91% yield (Scheme 8). Formation of the C2-acetal center was ascertained by a ^{13}C NMR signal at δ = 101.0 ppm ($CDCl_3$). Soft activation of **24**, using I_2 and Ag_2O, induced the reaction with the epicatechin unit **25**, giving the trimer **26** in 96% yield. The regio- and stereochemistry of the annulation was verified by extensive NMR studies.[12]

In the endgame, two silyl groups were removed by employing a large excess of nBu$_4$NF. One of the silyl groups



Scheme 8. Synthesis of (+)-cinnamtannin B_1 (**2**). Reaction conditions and reagents: a) $BF_3{\cdot}OEt_2$ (1.1 equiv), CH_2Cl_2, −78→−30 °C, 4 h (91%). b) I_2 (3 equiv), Ag_2O (1.5 equiv), 4 A M.S., CH_2Cl_2, −78→−40 °C, 2 h (96%). c) nBu$_4$NF (20 equiv), reflux, 16 h, THF (84%). d) H_2, ASCA2 [5% Pd(OH)$_2$/C], THF, MeOH, H_2O, RT, 2 h (83%).

was removed within 3 hours at room temperature, while the other silyl group was resistant. However, upon refluxing in THF for 16 hours, the silyl group was gradually removed to give the diol **27** in 84% yield. Finally, all benzyl groups and the bromine atom were simultaneously removed by the method described above (see Scheme 6). Anaerobic filtration (glass-fiber filter) under an inert atmosphere (argon) and partial concentration followed by reverse-phase column chromatography (Cosmosil 140C18-OPN, MeOH/H_2O = 0:100→30:70) and lyophilization gave (+)-cinnamtannin B_1 (**2**) as a snow-white solid (83% yield), which was identical with an authentic sample[25] as determined by direct comparison (^{1}H and ^{13}C NMR spectroscopy, IR, high resolution ESI-MS, HPLC);[12] The optical rotation was $[\alpha]_D^{25}$ = +64 (c = 0.31, MeOH) {lit.[1b] $[\alpha]_D$ = +69.2 (c = 0.99, MeOH)}.

In conclusion, a viable high-yielding and stereoselective synthetic approach to A-type procyanidins has been developed. Further studies along these lines are in progress in our laboratory.

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[12] See the Supporting Information.

[13] Annulation of the 2,4-bis(2-ethoxyethoxy) derivative with **9** (−78 → −20 °C, over 3 h) also proceeded smoothly, thus giving **11** in 79% yield.

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[19] CCDC 996429 (**21**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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