Bio-inspired polyene cyclization: synthesis of tetracyclic terpenoids promoted by steroidal acetal–$SnCl_4$†

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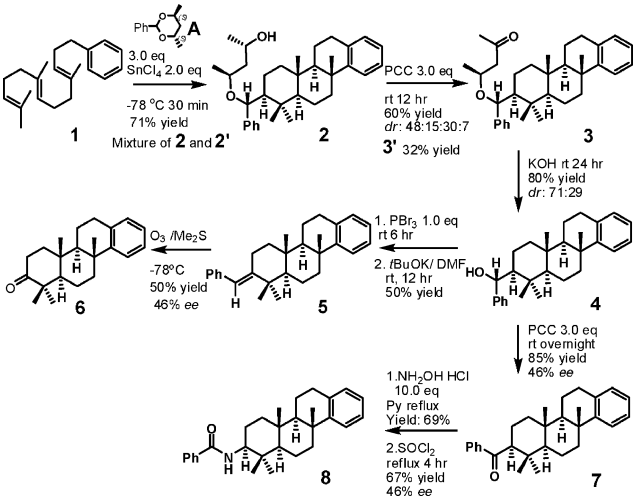
This communication describes a highly efficient intermolecular polyene cyclization method using steroidal acetals as the initiators to synthesize tetracyclic terpenoids; both good yields and good asymmetric induction were obtained.

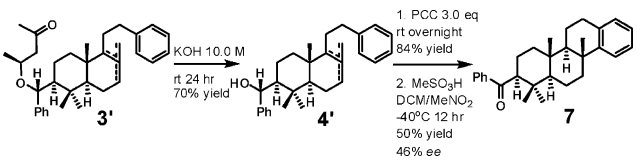
Multiple ring formation using polyene cyclization reactions is a powerful method for the preparation of alicyclic compounds.[1,2] A host of examples of polyene cyclization reactions for the synthesis of bicyclic and tricyclic compounds have been established, but reactions for forming tetracyclic compounds and above are still rare.[1–3] Furthermore, polyene cyclization reactions are attractive for the synthesis of molecules containing highly substituted C–C bonds.[1,2] Recently, Yamamoto *et al.* have demonstrated that chiral LBA (Lewis acid-assisted Brønsted acid) catalysts can be used to construct multiple rings with high enantioselectivities.[4] Ishihara *et al.* have also elegantly established a highly enantioselective polyene cyclization reaction promoted by a chiral electrophilic halogen atom.[5g] However, using polyene cyclization reactions to construct molecules containing more than three rings continues to pose a challenge to organic chemists. Herein, we describe the application of our previously reported approach[6] to a more challenging synthetic problem by using chiral aldehyde acetal and chiral acetal as a template to promote diastereoselective cyclization of polyprenoids to form tetracyclic terpenoids.

In the presence of $SnCl_4$, it was found that chiral acetal **A** promoted polyene **1** to furnish tetracyclic compound **2** with good yield and moderate diastereoselectivity (71% yield, dr: 48 : 15 : 30 : 7)[7,8] (see Scheme 1). The cyclization product can be easily modified to afford terpenoid **6** and 3-azaterpenoid[5] **8** with good enantioselectivity (**6**, 46% ee; **8**, 46% ee). In addition, the bicyclic isomer product **3′** can also be easily converted to the desired product **7** as shown in Scheme 2.

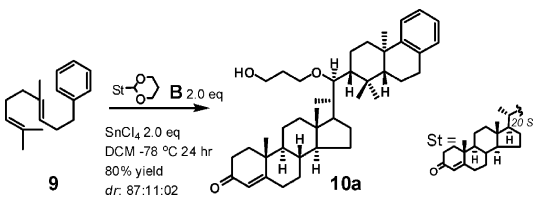
Next, we carried out the polyene cyclization reaction using chiral steroidal aldehyde **B** (StCHO) acetal as the initiator. To our delight, it was found that the oxonium generated from the aliphatic acetal was also efficient in initiating the cyclization of polyene **9**. The desired product **10a** was obtained in excellent yield (80%) with good diastereoselectivity (87 : 11 : 2) (see Scheme 3).



Scheme 1 The formation of tetracyclic terpenoids using PhCHO chiral acetal.‡



Scheme 2 Modification of bicyclic cyclization isomers.



Scheme 3 Cyclization promoted by steroidal acetal as the initiating group.‡

Further investigation showed that this cyclization method can also be applied to longer chain polyprenoid substrates to construct tetracyclic terpene skeletons (refer to Table 1). With different substituents on the benzene ring, all cyclization products were obtained in good yields and moderate diastereoselectivities.

For mechanistic interest, we further proceeded to investigate the effect of chirality of the 1,3-dioxane moiety on the cyclization diastereoselectivity. Therefore, the reactions were carried out using different steroidal acetals (**C** and **D**) with opposite

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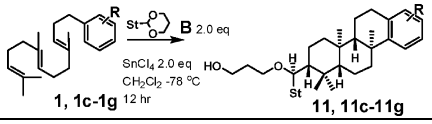
† Electronic supplementary information (ESI) available: Detailed experimental procedures, ^1H NMR, ^{13}C NMR and analytical data for all compounds. See DOI: 10.1039/b714474a

Table 1 Cyclization with different substituents on benzene substrates using steroidal acetal template‡

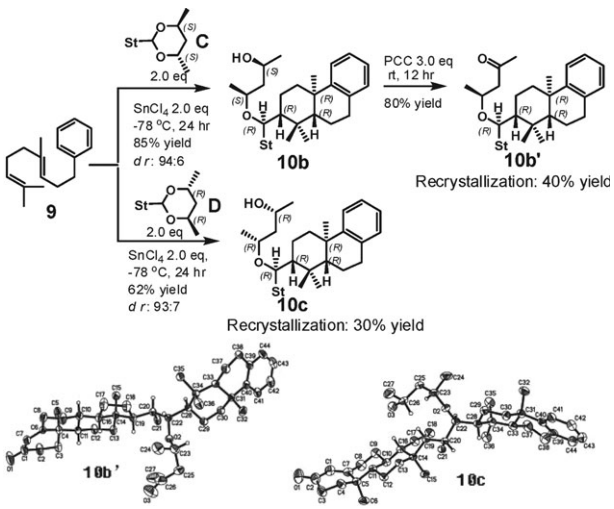


Entry	R	Product	Yield (%)[a]	dr[b]
1	—	**11**	73	66 : 18 : 10 : 6
2	4-Me	**11c**	66	66 : 17 : 14 : 3
3[c]	3-Me	**11d**	75	73 : 14 : 12 : 1
4	2-Me	**11e**	76	71 : 20 : 8 : 1
5	4-OMe	**11f**	59	74 : 18 : 7 : 1
6	4-*i*Pr	**11g**	71	64 : 20 : 14 : 2

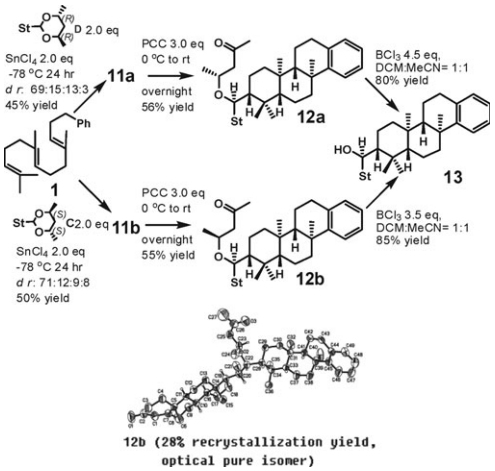
[a] Isolated yield of four isomers after flash chromatography. [b] Cyclization products were converted to corresponding aldehydes, the values of dr were determined based on the integration ratio of CHO peaks in the ^{1}H NMR spectra. [c] No regioisomers of the benzene ring were detected.[4b]

chirality on the 1,3-dioxane moiety (see Scheme 4). To our surprise, the absolute stereochemistries of both cyclization products shared the same trend, despite the chirality of the 1,3-dioxane moiety in the acetal being opposite. This result suggested that the chirality of the steroidal aldehyde played a dominant role in the control of the stereochemistry of the cyclization. It is worth noting that cyclization products and their derivatives can be obtained in optically pure isomers after single recrystallization (**10b′**, 40% yield; **10c**, 30% yield).

Extension of this method to the polyene cyclization of **1** afforded the tetracyclic products in moderate yields (**11a**, 45%; **11b**, 50%). Similar stereochemistries were observed for both **12a** and **12b**. This confirmed that the chirality of the steroidal aldehyde played a vital role in the control of the stereochemistry of the cyclization. It was notable that a single recrystallization of the oxidation product **12b** afforded the optically pure isomer in 28% yield (see Scheme 5).

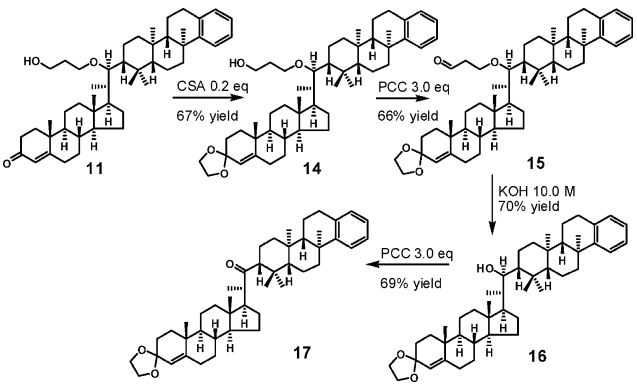


Scheme 4 (Top) Chiral induction comparison between 1,3-dioxane and aldehyde chirality.‡ (Bottom) X-Ray crystallographic structures of the major isomers of **10b′** (left) and **10c** (right). The ellipsoids are shown at the 50% probability level.[9]



Scheme 5 (Top) Verification of the steroidal aldehyde template effect.‡ (Bottom) Representative X-ray crystallographic structure of the major isomer of **12b**. The ellipsoids are shown at the 50% probability level.[9]

The cyclization products promoted by steroidal acetal–$SnCl_4$ are unique as the two biomolecules, steroid and terpenoid, are connected together through a C–C bond. It is also notable that cyclization products are versatile intermediates which can be readily converted to diverse tetracyclic terpenoids compounds bearing the steroid moiety as shown in Scheme 6.



Scheme 6 Functionalization of a cyclization product.[10]

In conclusion, we have reported a diastereoselective intermolecular polyene cyclization mediated by steroidal acetal–$SnCl_4$ to construct multiple ring terpene skeletons. The products were obtained in good yields and good diastereoselectivities. Investigations into diverse syntheses with different chiral templates and the application of this method to the total syntheses of natural products are in progress.

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Notes and references

‡ ***Representative procedure***: steroidal aldehyde–$SnCl_4$ promoted acetal cyclization reactions: to a solution of alkene **9** (22.4 mg, 0.1 mmol, 1.0

eq.) in DCM (2 mL) was added acetal **B** (78.0 mg, 0.2 mmol, 2.0 eq.) at room temperature. The solution was cooled to −78 °C prior to the addition of $SnCl_4$ (1.0 M in DCM, 0.2 mL, 2.0 eq.). The reaction was allowed to stir at −78 °C for 24 h before quenching with saturated $NaHCO_3$ aqueous solution (5 mL). The mixture was gradually warmed up to room temperature and was allowed to stir for another 1 h. The aqueous layer was extracted with DCM (3 × 20 mL), and the combined organic layer was washed with water (20 mL), brine (20 mL) and dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford desired product **10a** as a white solid in 80% yield (mixture of isomers). Isomer ratio: 87 : 11 : 2 (based on derivate aldehyde ^{1}H NMR integration). R_f: 0.18 (hexane–ethyl acetate, 4 : 1). Major isomer: ^{1}H NMR (500 MHz, $CDCl_3$): 7.38–7.02 (m, 4H), 5.75 (s, 1H), 3.90–3.70 (m, 3H), 3.70–3.50 (m, 1H), 3.45–3.35 (m, 1H), 2.97 (dd, J = 17.03, 5.58 Hz, 1H), 2.90–2.80 (m, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 1.20 (s, 3H), 0.95 (d, J = 6.80 Hz, 3H), 0.94 (s, 3H), 0.72 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 199.7, 171.6, 149.9, 135.0, 128.8, 125.7, 125.2, 124.5, 123.8, 80.6, 72.5, 63.1, 55.8, 53.7, 53.6, 53.3, 52.2, 45.1, 42.4, 39.6, 39.0, 38.6, 37.8, 37.3, 35.7, 35.7, 34.0, 32.9, 32.4, 32.0, 30.8, 29.5, 28.6, 25.2, 24.3, 21.0, 20.9, 19.2, 18.0, 17.4, 12.7, 11.7. HRMS (CI): m/z calculated for $C_{42}H_{62}O_3$ $[M]^+$: 614.4699, found $[M - H]^+$: 613.4521. FTIR (NaCl): ν 3436 (b), 1658, 1616, 1448, 1436, 1377, 1265, 1230 cm^{-1}.

Oxidation of cyclization products: To an oven-dried round-bottomed flask equipped with a magnetic stirring bar was added pyridinium chlorochromate (PCC) (65 mg, 0.3 mmol, 3.0 eq.), 4 Å molecular sieves (0.1 g), silica gel (0.1 g) and DCM (10 mL). A solution of alcohol **10a** (61 mg, 0.1 mmol, 1.0 eq. in 5 mL of DCM) mixture was added *via* syringe at 0 °C. The mixture was allowed to warm up to room temperature and stirred for 12 h until the reaction had finished. The reaction solution was filtered through a pad of silica gel packed in a sintered funnel and washed with ethyl acetate (100 mL). The filtrate was concentrated *in vacuo*. The residual crude product was purified by flash column chromatography to afford aldehyde **10a′** as a white solid in 80% yield. Isomer ratio: 87 : 11 : 2 (CHO ^{1}H NMR integration) R_f: 0.23 (hexane–ethyl acetate, 4 : 1). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$): 9.84 (t, J = 2.07 Hz, 1H), 7.29–7.22 (m, 1H), 7.16–7.09 (m, 1H), 7.09–7.00 (m, 2H), 5.73 (s, 1H), 3.87 (dt, J = 8.60, 5.87 Hz, 1H), 3.74 (dt, J = 9.12, 6.40 Hz, 1H), 3.42 (m, 1H), 2.95 (dd, J= 16.78, 5.87 Hz, 1H), 2.90–2.80 (m, 1H), 2.65–2.60 (m, 2H), 1.20 (s, 3H), 1.19 (s, 3H), 0.94 (s, 3H), 0.93 (s, 3H), 0.91 (d, J = 6.91 Hz, 3H), 0.70 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 201.9, 199.6, 171.6, 149.9, 135.0, 128.8, 125.7, 125.2, 124.5, 123.8, 80.0, 65.6, 55.8, 53.7, 53.5, 53.3, 52.2, 45.1, 44.5, 42.4, 39.6, 39.1, 38.6, 37.8, 37.3, 35.7, 35.6, 34.0, 33.0, 32.0, 30.9, 29.5, 28.6, 25.3, 24.3, 21.0, 20.8, 19.2, 18.0, 17.4, 12.5, 11.7. HRMS (CI): m/z calculated for $C_{42}H_{60}O_3$ $[M]^+$: 612.4542, found: not obtained. FTIR (NaCl): ν 1654 (b), 1448, 1375, 1228, 1186, 1097 cm^{-1}.

Theoretically, four possible isomers were formed (for detailed structures see ESI†). For Scheme 1, dr refers to diastereomer ratio, see ref. 7 and 8; for Scheme 3, cyclization products were converted to the corresponding aldehyde, and the dr was determined based on the integration ratio of CHO peaks in the ^{1}H NMR spectra.

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7 dr = diastereoisomer ratio. For Scheme 1 dr were reported as the benzylic isomer ratio based on ^{1}H NMR integration of benzylic CHs.

8 For Scheme 1, diastereomers here refer to isomers with different relative configuration between the chiral center(s) on the benzylic carbon and the five new chiral centers formed in the tricyclic skeleton. The five new chiral centers formed are considered as one chiral group (of fixed relative configuration within the group) based on the Stork–Eschenmoser postulate. See: (*a*) G. Stork and A. W. Burgstahler, *J. Am. Chem. Soc.*, 1955, **77**, 5068; (*b*) A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta*, 1955, **38**, 1890. For all other cases, the assignment of diastereoisomers for Scheme 1 applied as well.

9 For **10b′**, **10c**, **12b**: CCDC 661546, 661547 and 661548. For crystallographic data in CIF format see DOI: 10.1039/b714474a.

10 The regioisomer ratio is reported in the ESI.† The isomerization of the double bond was reported by De Leeuw, *et al.*: J. W. De Leeuw, E. R. De Waard, T. Beetz and H. O. Huisman, *Recl. Trav. Chim. Pays-Bas*, 1973, **92**, 1047.

