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A [2+2+2]-cyclotrimerization approach for the synthesis of enantiopure isochromans using a carbohydrate derived dialkyne template

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Abstract

An easy access to enantiopure isochromans through cross alkyne trimerization of a glucose derived dialkyne was developed. One of the synthesized isochromans was converted into a novel tricyclic nucleoside by simple transformations.

Keywords: Isochroman; [2+2+2]-Cyclotrimerization; Wilkinson's catalyst; Vorbrüggen reaction; Tricyclic nucleoside

Designing effective routes to construct complex cyclic structures through organo transition-metal catalyzed reactions has been recognized as an attractive strategy for delivering molecular diversity.[1] Integrated with transition-metal catalyzed reactions, sugar templates have been well deployed to address the synthesis of a variety of complex natural product skeletons.[2] Amongst the many other metal catalyzed reactions which have been explored on sugar templates, catalytic [2+2+2]-alkyne cyclotrimerizations are important as they deliver highly functionalized aromatic rings appended with sugar rings.[3] An early example in this context is an expedient total synthesis of the spirocyclic *C*-arylglycoside framework closely related to the papulacandins by McDonald et al. utilizing a rhodium(I)-catalyzed [2+2+2]-cyclotrimerization[4] which has been well explored with various sugar derivatives.[5] Considering the simplicity of the [2+2+2]-alkyne cyclotrimerization combined with our current interest in exploiting carbohydrates for constructing useful molecular diversity,[6] herein, we report the synthesis of enantiomeric tricyclic molecular skeletons consisting of isochroman units (Fig. 1).

Isochroman (**1**, 3,4-dihydro-1*H*-benzo[*c*]pyran) is a structural unit found in some important biologically active compounds, commercially available drugs and cosmetics.[7] Several synthetic 6,7-dimethoxyisochromans and their 1-arylated analogues have been disclosed as new investigational drugs with a wide range of activities such as analgesic, muscle relaxant, antidepressant, anti-inflammatory, antihistaminic, anticoagulant and antihypertensive.[8]

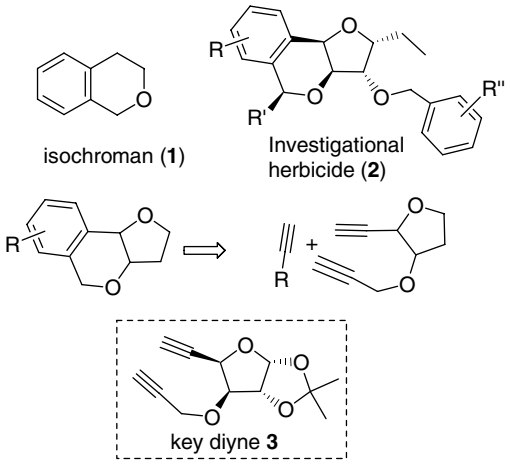

Fig. 1. Key [2+2+2]-cyclotrimerization approach for enantiopure isochromans.

Kakimoto et al. prepared a series of tricyclic isochroman derivatives **2** from glucose and evaluated their herbicidal

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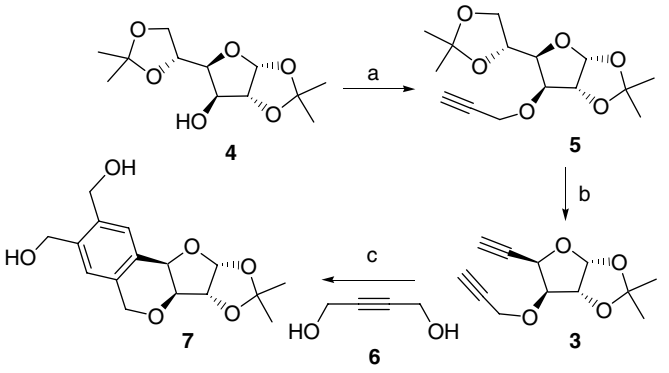
activities.[9] A number of synthetic methods involving electrophilic reactions mediated by Lewis acids, radical and carbanion-mediated annulations, and cycloadditions have been reported for the synthesis of isochroman units.[7] The oxa-Pictet–Spengler condensation is a widely used method for the preparation of isochroman units.[7b] An expedient approach for sugar annulated isochromans by Martin et al. using intramolecular Friedel–Crafts cyclization has been reported.[10] Recently, Kaliappan and Ravikumar reported an intramolecular enyne-metathesis and subsequent trapping of the resulting dienes by various quinones for the synthesis of tetracyclic derivatives containing an isochroman ring.[11]

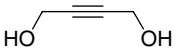
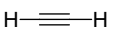
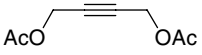
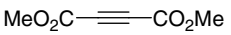
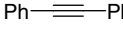
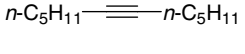
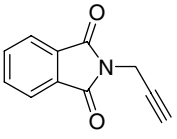
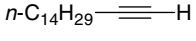
Our intended strategy is described in Figure 1. The synthesis of the key diyne **3** started with the propargylation of glucose diacetonide **4** to procure the propargyl ether **5**.[12] Selective monoacetonide hydrolysis of **5** followed by sodium periodate mediated cleavage and subsequent Ohira–Bestmann alkynylation[13] of the intermediate aldehyde provided **3** in 49% overall yield (Scheme 1). With the fully elaborated diyne framework **3** in place, cyclotrimerization was attempted with 2-butyne-1,4-diol (**6**). After a careful examination of some of the catalysts reported for



Scheme 1. Reagents and conditions: (a) NaH, propargyl bromide, THF, 0 °C to rt, 8 h, 89%; (b) (i) 0.8% H_2SO_4, MeOH, rt, 24 h; (ii) $NaIO_4$–silica gel, CH_2Cl_2, rt, 1 h; (iii) $(MeO)_2P(=O)C(=N_2)COCH_3$, methanol, K_2CO_3, rt, 7–9 h, 49% for three steps; (c) $Rh(PPh_3)_2Cl$, toluene–ethanol (4:1), 80 °C, 8 h, 61%.

[2+2+2]-alkyne cyclotrimerization, we found that Wilkinson's catalyst afforded the tricyclic derivative **7** in good yields.[5d] The spectral and analytical data of **7** were in accordance with the assigned structure.[14] For example, in the ^1H NMR spectrum of **7**, the two aromatic-H appeared

Table 1

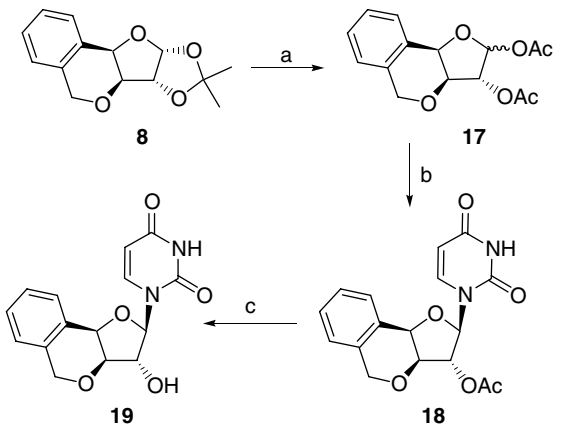
Entry	Alkyne	Product(s)	Yield (%)
1		**7** (R = R′ = CH_2OH)	61
2		**8** (R = R = H)	65
3		**9** (R = R′ = CH_2Oac)	57
4		**10** (R = R′ = CO_2Me)	45
5		No reaction	
6		No reaction	
7		No reaction	
8		**11** (R = Ph, R′ = H) **12** (R = H, R′ = Ph) (1:3)	72
9		**13** (R = CH_2NPhth, R′ = H) **14** (R = H, R′ = CH_2NPhth) (2:3)	67
10		**15** (R = *n*-$C_{14}H_{29}$, R′ = H) **16** (R = H, R′ = *n*-$C_{14}H_{29}$) (1:1)	49

as singlets at δ 6.99 and δ 7.24 ppm. The characteristic C(1)–H and C(2)–H of the furanose ring appeared as doublets at δ 5.92 and 4.70 ppm ($J_{1,2} = 3.8$ Hz), respectively. C(4)–H appeared downfield (δ 4.89 ppm) as a doublet with $J = 2.3$ Hz. The observed cross peaks in the NOESY spectrum between C(4)–H and the aromatic ring proton at δ 7.24 ppm were indicative of a possible anisotropic effect of the furanose ring oxygen, which helped in assigning the ratios of the regiomeric compounds resulting from unsymmetric alkynes. The presence of two methyleneoxy groups at δ 62.7 and 66.9 ppm in the ^{13}C NMR further confirmed the assigned structure.

To illustrate the flexibility of our strategy, various alkynes were employed in the [2+2+2]-cyclotrimerization and the results are summarized in Table 1. With acetylene, the cyclotrimerization reaction proceeded effectively at 80 °C in a sealed tube to afford **8** in good yield.[15] Unsymmetrical alkynes such as phenylacetylene and hexadec-1-yne gave inseparable regiomeric mixtures in moderate to good yields (Table 1).

Having established the feasibility of the [2+2+2]-cyclotrimerization for the synthesis of sugar annulated isochromans, we next applied isochroman **8** for the synthesis of modified nucleoside **19**. As shown in Scheme 2, isochroman **8** was subjected to acid catalyzed acetonide hydrolysis using acetic acid followed by acetylation in dichloromethane, acetic anhydride and Et_3N to afford a 1:1 anomeric mixture of **17**. Treatment of **17** with uracil under modified Vorbrüggen[16] conditions afforded the protected nucleoside **18**.[17] Subjecting **18** to Zemplen's deacetylation gave the tricyclic nucleoside **19**. The structure of **19**[18] was established with the help of COSY and NOESY spectra that confirmed the assigned β-configuration for **19** beyond doubt.

To conclude, a general synthesis of chiral isochromans via [2+2+2]-cyclotrimerization of a sugar template as the key reaction was reported. One of the derived isochromans was converted into a tricyclic nucleoside by simple synthetic manipulations. Considering the importance of conformationally restricted nucleosides as antiviral agents and as potential antisense therapeutic and diagnostic agents, the results from the present investigation could be further explored for a strategic construction of these molecular skeletons. Work in this direction is ongoing in our laboratory.



Scheme 2. Reagents and conditions: (a) (i) 60% AcOH, reflux, 2 h, 92%; (ii) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1 h, 94%; (b) uracil, *N*,*O*-bis(trimethylsilyl)acetamide (BSA), TMSOTf, CH_3CN, 50 °C, 2 h, 79%; (c) NaOMe, MeOH, rt, 20 min, 96%.

Acknowledgements

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14. *Spectral data of compound* **7**: $[\alpha]_D^{25}$ 28.0 (*c* 1.2, $CHCl_3$). IR ($CHCl_3$) *v*: 3401, 3016, 2933, 1734, 1513, 1452, 1438, 1376, 1247, 1216, 1163, 1118, 1102, 1080, 1017, 898, 857, 830, 755, 667 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 1.35 (s, 3H), 1.58 (s, 3H), 3.90 (br s, 2H), 4.09 (d, $J = 2.3$ Hz, 1H), 4.47–4.60 (m, 5H), 4.67 (d, $J = 3.8$ Hz, 1H), 4.70 (d, $J = 15.1$ Hz, 1H), 4.89 (d, $J = 2.3$ Hz, 1H), 5.92 (d, $J = 3.8$ Hz, 1H), 6.99 (s, 1H), 7.24 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.1 (q), 26.7 (q), 62.7 (t), 66.9 (t), 73.1 (d), 79.8 (d), 84.4 (d), 104.9 (d), 111.7 (s), 124.6 (d), 128.4 (s), 130.9 (d), 132.1 (d), 134.4 (s), 138.2 (s), 140.2 (s) ppm. ESI-MS *m/z*: 301.26 (100%), 309.36 (2.3%, $[M+1]^+$), 331.32 (89.2%, $[M+Na]^+$), 347.30 (3.5%, $[M+K]^+$). Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.12; H, 6.68.
15. *Spectral data of compound* **8**: $[\alpha]_D^{25}$ 21.6 (*c* 1.5, $CHCl_3$). IR ($CHCl_3$) *v*: 3018, 2927, 1458, 1376, 1216, 1164, 1116, 1091, 1020, 920, 754, 666 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.28 (s, 3H), 1.50 (s, 3H), 4.06 (d, $J = 2.4$ Hz, 1H), 4.55–4.75 (m, 3H), 4.87 (d, $J = 2.3$ Hz, 1H), 5.89 (d, $J = 3.91$ Hz, 1H), 6.94–7.01 (m, 1H), 7.17–7.25 (m, 2H), 7.35–7.41 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 26.3 (q), 26.9 (q), 67.4 (t), 73.5 (d), 80.1 (d), 84.7 (d), 105.2 (d), 111.6 (s), 124.2 (d), 127.4 (d), 128.7 (d), 129.5 (s), 130.7 (d), 134.8 (s) ppm. ESI-MS: *m/z* 266.32 (35.9%, $[M+NH_4]^+$), 271.29 (100%, $[M+Na]^+$). Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.44; H, 6.89.
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17. *Spectral data of compound* **18**: $[\alpha]_D^{25}$ −8.6 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) *v*: 3032, 2927, 1750, 1682, 1461, 1371, 1320, 1268, 1225, 1108, 1066, 909, 78, 761, 734, 667, 602 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 2.17 (s, 3H), 4.18 (d, $J = 2.6$ Hz, 1H), 4.71 (d, $J = 15.16$ Hz, 1H), 4.86 (d, $J = 15.16$ Hz, 1H), 4.95 (d, $J = 2.5$ Hz, 1H), 5.22 (d, $J = 1.6$ Hz, 1H), 5.60 (dd, $J = 2.1$, 8.2 Hz, 1H), 6.15 (d, $J = 1.6$ Hz, 1H), 7.11 (dd, $J = 2.1$, 8.2 Hz, 1H), 7.32–7.48 (m, 4H), 9.21 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 20.7 (q), 67.3 (t), 75.4 (d), 78.8 (d), 81.7 (d), 89.3 (d), 102.5 (d), 124.4 (d), 127.82 (d), 127.9 (s), 129.4 (d), 130.6 (d), 134.1 (s), 140.5 (d), 150.2 (s), 163.1 (s), 169.2 (s) ppm. ESI-MS: *m/z* 344.09 (5.11%, $[M]^+$), 367.02 (100%, $[M+Na]^+$). Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.03; H, 4.90; N, 7.97.
18. *Spectral data of compound* **19**: $[\alpha]_D^{25}$ 60.4 (*c* 1.9, $CHCl_3$). IR ($CHCl_3$) *v*: 3383, 3218, 3108, 3068, 2923, 2844, 2252, 1775, 1695, 1493, 1464, 1408, 1393, 1373, 1360, 1322, 1265, 1206, 1114, 1097, 1076, 1059, 999, 960, 908, 877, 813, 788, 733, 649 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 4.22 (d, $J = 1.9$ Hz, 1H), 4.52 (s, 1H), 4.64 (d, $J = 15.1$ Hz, 1H), 4.72 (d, $J = 15.1$ Hz, 1H), 5.24 (d, $J = 1.9$ Hz, 1H), 5.48 (d, $J = 8.0$ Hz, 1H), 5.65 (s, 1H), 5.89 (s, 1H), 7.1 (dd, $J = 2.3$, 8.1 Hz, 1H), 7.15 (d, $J = 8.03$ Hz, 1H), 7.34–7.36 (m, 2H), 7.46 (dd, $J = 2.3$, 8.1 Hz, 1H), 10.61 (br s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 66.9 (t), 77.1 (d), 80.1 (d), 80.7 (d), 94.2 (d), 101.1 (d), 124.3 (d), 127.8 (d), 128.8 (s), 129.2 (d), 130.8 (d), 134.3 (s), 140.7 (d), 151.1 (s), 164.2 (s) ppm. ESI-MS: *m/z* 325.01 (100%, $[M+Na]^+$), 340.99 (7.3%, $[M+K]^+$). Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.33; H, 4.92; N, 8.99.