

A [2+2+2]-cyclootrimerization 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.

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Keywords: Isochroman; [2+2+2]-Cyclootrimerization; 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-aryl glycoside framework closely related to the papulacandins by McDonald et al. utilizing a rhodium(I)-catalyzed [2+2+2]-cyclootrimerization⁴ 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

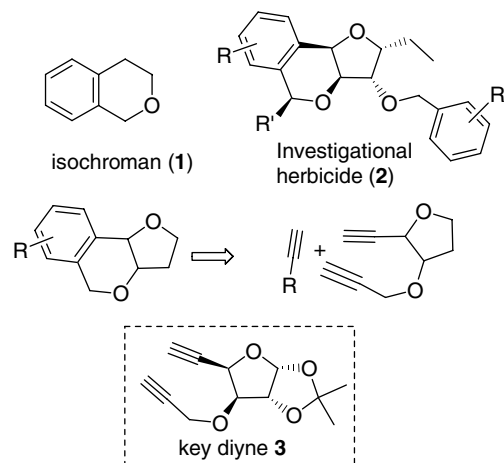


Fig. 1. Key [2+2+2]-cyclootrimerization approach for enantiopure isochromans.

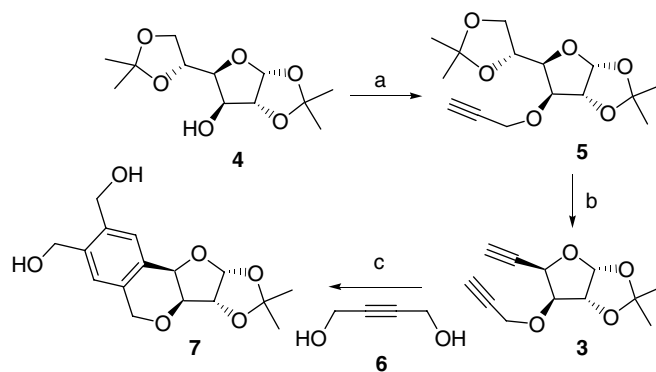
compounds, commercially available drugs and cosmetics.⁷ Several synthetic 6,7-dimethoxyisochromans and their 1-arylated analogues have been disclosed as new investigational drugs with a wide range of activities such as analgesic, muscle relaxant, antidepressant, anti-inflammatory, antihistaminic, anticoagulant and antihypertensive.⁸

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 alkynylation¹³ 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% H₂SO₄, MeOH, rt, 24 h; (ii) NaIO₄–silica gel, CH₂Cl₂, rt, 1 h; (iii) (MeO)₂P(=O)C(=N₂)COCH₃, methanol, K₂CO₃, rt, 7–9 h, 49% for three steps; (c) Rh(PPh₃)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 ₂ OH)	61
2		8 (R = R = H)	65
3		9 (R = R' = CH ₂ OAc)	57
4		10 (R = R' = CO ₂ Me)	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 ₂ NPhth, R' = H) 14 (R = H, R' = CH ₂ NPhth) (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 regiomer 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 regiomer 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 Vorbrüggen¹⁶ 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 con-

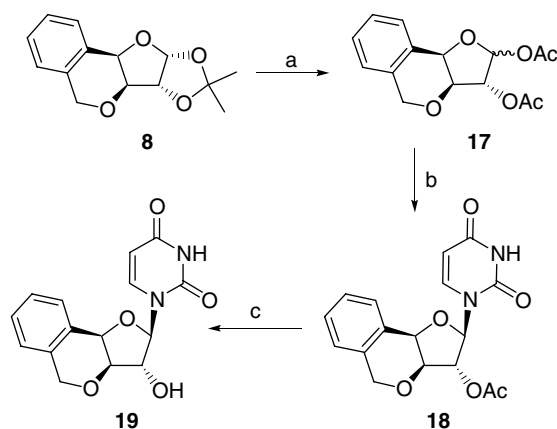
formationally restricted nucleosides as antiviral agents and as potential antisense therapeutic and diagnostic agents, the results from the present investigation could be further explored for a strategic construction of these molecular skeletons. Work in this direction is ongoing in our laboratory.

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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%.

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14. *Spectral data of compound 7*: $[\alpha]_{\text{D}}^{25}$ 28.0 (*c* 1.2, CHCl₃). IR (CHCl₃) ν : 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, CDCl₃) 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). ¹³C NMR (50 MHz, CDCl₃) 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 C₁₆H₂₀O₆: C, 62.33; H, 6.54. Found: C, 62.12; H, 6.68.
15. *Spectral data of compound 8*: $[\alpha]_{\text{D}}^{25}$ 21.6 (*c* 1.5, CHCl₃). IR (CHCl₃) ν : 3018, 2927, 1458, 1376, 1216, 1164, 1116, 1091, 1020, 920, 754, 666 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) 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). ¹³C NMR (50 MHz, CDCl₃) 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+NH₄]⁺), 271.29 (100%, [M+Na]⁺). Anal. Calcd for C₁₄H₁₆O₄: C, 67.73; H, 6.50. Found: C, 67.44; H, 6.89.
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17. *Spectral data of compound 18*: $[\alpha]_{\text{D}}^{25}$ -8.6 (*c* 1.0, CHCl₃). IR (CHCl₃) ν : 3032, 2927, 1750, 1682, 1461, 1371, 1320, 1268, 1225, 1108, 1066, 909, 78, 761, 734, 667, 602 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) 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). ¹³C NMR (50 MHz, CDCl₃) 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 C₁₇H₁₆N₂O₆: 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*: $[\alpha]_{\text{D}}^{25}$ 60.4 (*c* 1.9, CHCl₃). IR (CHCl₃) ν : 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, CDCl₃) 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). ¹³C NMR (50 MHz, CDCl₃) 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 C₁₅H₁₄N₂O₅: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.33; H, 4.92; N, 8.99.