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The enantiospecific synthesis of chromanes and isochromanes using a variant of an intramolecular Nicholas reaction

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ABSTRACT

The enantiospecific synthesis of chromanes and isochromanes obtained from an intramolecular Nicholas cyclisation reaction is discussed. During the course of this study we observed the formation of chroman-4-ones from a CAN deprotection step of a dioxolane and this is also discussed.

Previously we described the antihypertensive activity of a range of novel chromanes,[1] synthesised using a variation of an intramolecular Nicholas reaction[2] that has been developed, over a number of years, in our laboratories.[3] The assay involved isometric tension recordings on segments of mouse thoracic aorta. After an initial period of equilibration the tissues were contracted by application of the α-1-adrenoceptor stimulant, phenylephrine. Once the contraction had stabilised our compounds were evaluated by comparing their ability to relax the pre-contracted tissue versus the benchmark compound cromakalim (**1**).[4] The best candidate (**2**) is shown (Fig. 1).

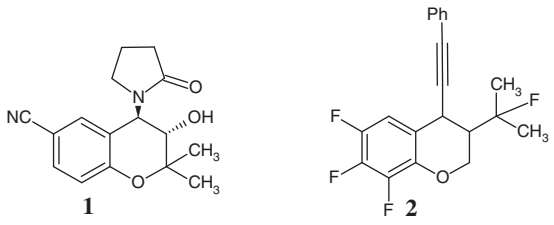
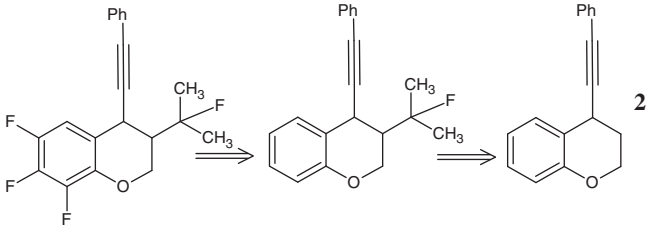


Figure 1.

Although the derivatives that were synthesised retained some of the pharmacophores, present in cromakalim (**1**), it was no surprise that our best candidate **2** failed to replicate the same response as **1**. It was active at the 20 μM scale compared to cromakalim **1** which provided the same level of relaxation of the tissue at the 1 μM level. It was observed, however, that when the same assay was carried out in the presence of glibenclamide, a selective blocker of ATP-sensitive K^+ channels, chromane **2** continued to produce relaxation of the contracted mouse thoracic tissue whereas cromakalim (**1**) was ineffective. This observation therefore suggested two different modes of action for these molecules.



Scheme 1.

The potassium channel modulating properties of cromakalim (**1**) have been well documented.[5] In collaboration with colleagues at St. George's Hospital Medical School we have been investigating the possible modes of action of these novel chromanes. One line of enquiry is the possibility that they may be involved in alternative ion-selective membrane channels such as chloride channels. Compared to potassium channels, the mechanisms of action of chloride channels are less well understood despite the fact that they are

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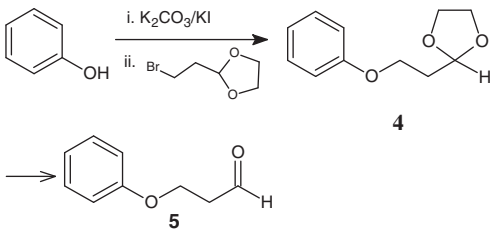
implicated in a wide range of physiological activities.[6] As part of our ongoing investigations into the structure–activity relationship of **1** we were keen to determine the structural features that were responsible for the selectivity we had observed. This would involve the synthesis of simpler derivatives that might act as probes during our investigations. Apart from the aryl substituents the main structural modification to be considered was the removal of the C-3 moiety to afford a chromane such as **3** (Scheme 1).

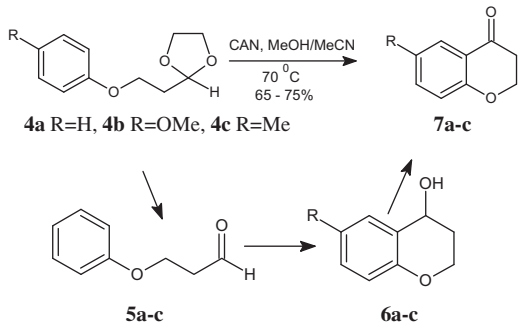
Another key aim in our ongoing screening investigations has been the development of asymmetric variants of the Nicholas reaction.[7] Our approach to the synthesis of **3** was via aldehyde **5** which, we reasoned, should be readily obtained from the deprotection of dioxolane **4** (Scheme 2).

An asymmetric Carreira alkynylation[8,9] of aldehyde **5** and cobalt complexation followed by a Friedel-Crafts variant of the Nicholas cyclisation[10,11] should, after the oxidative decomplexation of dicobalt hexacarbonyl, afford the desired chromane **3** in an enantiomeric enriched form. Thus O-alkylation of phenol with 2-(2-bromoethyl)-1,3-dioxane[12] provided the corresponding dioxalane **4a** (90%) (Scheme 3). Our attempts to deprotect **4a** were thwarted by variable yields of the desired product **5a**, substrate and decomposition products.[13] A recent publication described the use of cerium ammonium nitrate (CAN) for the deprotection of a wide range of dioxanes and dioxolanes under mild conditions.[14] Exposure of **4a** to CAN[15] led rapidly to the formation of a new product. Spectroscopic analysis failed to reveal the desired aldehyde **5a**, but instead showed the formation of chroman-4-one **7a** in a yield of 70%.

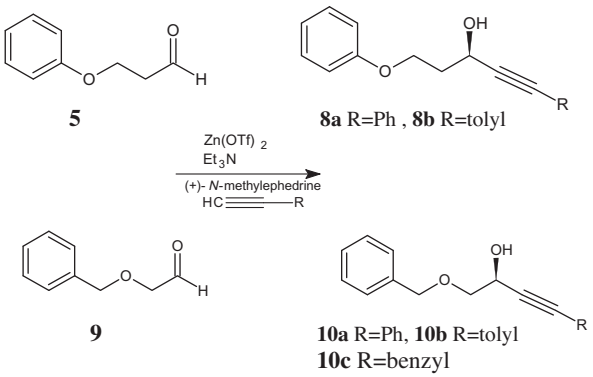
We reasoned that the origin of **7a** was from **5a**, via the alcohol **6a**. A survey of the literature confirmed that CAN oxidation of benzylic alcohols to ketones (in the presence of TEMPO) is not without precedent.[16] Although unexpected, this serendipitous outcome, in terms of an effective two-step formation of chroman-4-one **7a** directly from **4a** in the presence of CAN, and an absence of a catalyst such as TEMPO, may also be of synthetic interest.[17] We were able to optimise the production of aldehyde **5a** (55–70%) by reducing the exposure time of **4a** to one equivalent of CAN for 20 min,[18] any longer would provide either **6a** or **7a**. Although the formation was a distraction from our main aims we did investigate the production of chromanones, **7b** (75%) and **7c** (78%) derived from *p*-methoxyphenol and *p*-methylphenol, respectively.[19] With the aldehyde **5a** in hand, we undertook the asymmetric alkynylation reaction. Previously, we revealed that both the yield of the Carreira asymmetric alkynylation of aldehydes and the enantiomeric excess were variable. For instance, the asymmetric alkynylation of benzaldehyde occurred with a yield of 80% (ee 81%), *p*-bromobenzaldehyde 97% (ee 99%) and *p*-methoxybenzaldehyde 53% (ee 99%).[20] Furthermore, the reactions with non-aryl aldehydes were often slower, less efficient and occurred with reduced enantioselectivities.[21] Importantly, however, it has been demonstrated that the stereochemical outcome of the alkynylation reaction is dependent upon the choice of chiral ligand.[8,22] Thus the asymmetric alkynylation of aldehyde **5a**, with phenylethyne in the presence of (+)-*N*-methylephedrine, gave the corresponding propargyl alcohol **8a** in a yield of 77% and a disappointing enantiomeric excess of 50%. This result seems to



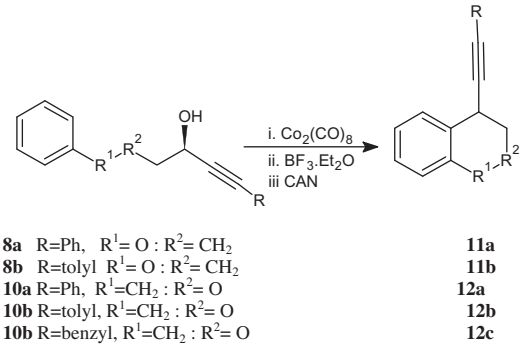
Scheme 2.



Scheme 3.



Scheme 4.



Scheme 5.

Table 1

Entry	Product	ee (%)	Product	ee (%)	(c.[24] ee%)
1	**8a**	50	**11a**	45	90
2	**8b**	74	**11b**	71	95
3	**10a**	81	**12a**	77	95
4	**10b**	82	**12b**	82	100
5	**10c**	77	**12c**	76	99
6[a]	**11b**	73	**13b**	71	97

[a] Obtained from the use of (−)-*N*-methylephedrine.

represent an outlier as our subsequent data reveals. The use of 4-ethynyltoluene provided **8b** in 74% yield and an ee of 74%.[23] The same reaction performed upon the readily available aldehyde **9** provided propargyl alcohols **10a** (89%, ee 81%), **10b** (90%, ee 82%) and **10c** (78%, ee 77%) (Scheme 4).

Propargyl alcohols **8a,b** and **10a–c** were then subjected to the Nicholas cyclisation reaction conditions (Scheme 5). This consisted of complexation with dicobalt octacarbonyl (70–85%), reaction with boron trifluoride diethyl etherate at −75 °C, to effect cyclisation, followed by decomplexation using CAN which provided the corresponding chromanes **11a,b** and isochromanes **12a–c** in good to excellent yields, that is 76% for **11a** to 90% for **12a**. The cyclised products were analysed by chiral HPLC and our first example **8a**, with the lowest enantiomeric excess (50%), provided the corresponding chromane **11a** with an ee of 45% (90% corrected).[24]

The data for the other cyclisation products are provided (Table 1)[25] which were all found to be consistently better than our prototype. Also included (entry 6), are data for **11b**, that is, the antipode to **10b**.

The data summarised in Table 1 serve to confirm that, apart from the outlier, (entry 1), the intramolecular Nicholas cyclisation reaction provides chiral chromanes and isochromanes from chiral substrates with a minimum loss in optical activity. During the course of these investigations, we additionally identified an efficient synthesis of chroman-4-ones from the CAN-mediated deprotection of a dioxolone.[26] Although the biological activity of the chromanes and isochromanes that were synthesised during the course of this study are currently underway, obtaining answers to the challenging questions such as the stereochemical relationships between the substrates and products continues to remain a high priority in our group.

Acknowledgments

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References and notes

1. Tyrrell, E.; Tesfa, K.-H.; Greenwood, I.; Mann, A. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1237–1240.
2. Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207–214; For a review please see: Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, *11*, 1657–1668; Teobold, B. J. *Tetrahedron* **2002**, *58*, 4133–4170.
3. Berge, J.; Claridge, S.; Mann, A. L.; Muller, C.; Tyrrell, E. *Tetrahedron Lett.* **1997**, *38*, 685–686; Tyrrell, E.; Millet, J.; Tesfa, K.-H.; Williams, N.; Mann, A. L.; Tillett, C.; Tyrrell, E. *Tetrahedron* **2007**, *63*, 12769–12778; Mann, A. L.; Muller, C.; Tyrrell, E. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1427–1438.
4. For reviews of cromakalim, see: Roxburgh, C. J. *Synthesis* **1996**, 307–320; Sebille, S.; De Tullio, P.; Boverie, S.; Antoine, M. H.; Lebrun, P. B. *Curr. Med. Chem.* **2004**, *11*, 1213–1222.
5. Hamilton, T. C.; Weir, S. W.; Weston, A. H. *Br. J. Pharmacol.* **1986**, *88*, 103–112; Ashcroft, F. M.; Gribble, F. M. *Trends Pharm. Sci.* **2005**, *21*, 439–444; Cechetti, V.; Tabarrini, O.; Sabatini, S. *Curr. Top. Med. Chem.* **2006**, *6*, 1049–1068.
6. Jentsch, T. J.; Stein, V.; Weinreich, F.; Zdebik, A. A. *Physiol. Rev.* **2002**, *82*, 503–568.
7. Unpublished results: Tyrrell, E.; Brawn, P.; Carew, M.; Greenwood, I. Tetrahedron, pending submission.
8. Franz, D. E.; Fassler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806–1807; Franz, D. E.; Fassler, R.; Tomooka, C. S.; Carreira, E. M. *Acc. Chem. Res.* **2000**, *33*, 373–381; Sasaki, H.; Boyall, D.; Carreira, E. M. *Helv. Chim. Acta.* **2001**, *84*, 964–971.
9. Tyrrell, E. *Curr. Org. Chem.* **2009**, *13*, 1540–1552.
10. Muehldorf, A. V.; Guzman-Perez, A.; Kluge, A. F. *Tetrahedron Lett.* **1994**, *35*, 8755–8758.
11. Grove, D. D.; Miskevich, F.; Smith, C. C.; Corte, J. R. *Tetrahedron Lett.* **1990**, *64*, 6277–6280.
12. We also made the corresponding dioxolane derivative.
13. Kocienski, P.J., *Protecting Groups*, **2000**, Thieme Verlag, Stuttgart. Classic acid hydrolysis failed and other methods proved equally unreliable, that is catalytic iodine: Sun, J.; Dong, L.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932–8934.
14. Maulide, N.; Vanherck, J.-C.; Gautier, A.; Marko, I. E. *Acc. Chem. Res.* **2007**, *40*, 381–393.
15. Dissolved in a 2:1 mixture of acetonitrile/water at 70 °C for 20 min.
16. Kim, S. S.; Jung, H. C. *Synthesis* **2003**, 2135–2137.
17. Benzopyranone syntheses *via* a Stetter reaction: Enders, D.; Breuer, K.; Runsink, J. *Helv. Chim. Acta.* **1996**, *79*, 1899–1902; Rong, Z. Q.; Li, Y.; Yang, G.-Q.; You, S-. L. *Synlett* **2011**, 1033–1037; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284–6289; He, J.; Zheng, J.; Liu, J.; She, X.; Pan, X. *Org. Lett.* **2006**, *8*, 4637–4640. and other references cited therein.
18. Aldehyde **5** was frequently contaminated with **6** and therefore required purification which reduced the yield further.
19. These investigations were carried out by P.S. as part of a summer internship.
20. Tyrrell, E.; Tesfa, K.-H.; Mann, A.; Singh, K. *Synthesis* **2007**, 1491–1498.
21. Tyrrell, E.; Tesfa, K.-H.; Millet, J.; Muller, C. *Synthesis* **2006**, 3099–3105.
22. Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687–9688.
23. Chiral HPLC was carried out using a (Chiralcel-OD-H column) with a Perkin Elmer 200 EP photodiode array diode detector. Measurements were made at 220 nm at a flow rate of 0.3 ml/min. Solvent, hexane/IPA (90/10).
24. The corrected enantiomeric excess[10] is determined as the ee of the product divided by the ee of the substrate expressed as a percentage.
25. All new compounds gave satisfactory spectroscopic data.
26. *Representative procedure:* 2,3-dihydro-4*H*-chromen-4-one (**7a**). To the dioxalane **4a** (1.20 g, 6.18 mmol) in an MeCN–H_2O mixture (10 ml, 1:2) was added CAN (5 g, 9.27 mmol). The mixture was heated to 70 °C, with stirring, for 30 min and then allowed to cool to ambient temperature. The organic solvent was partitioned in H_2O and extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with a saturated solution of $NaHCO_3$ (20 mL) and then dried over anhydrous $MgSO_4$. Filtration in vacuo gave the title compound as a yellow oil 0.64 g, 70%. ν_{max} (neat)/cm^{-1} 2923, 1688, 1603, 1479, 1299, 1255, 1119, 1039, 870, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (1H, dd, J = 7.85, 1.73 Hz, Ph), 7.50 (1H, ddd, J = 8.41, 7.16, 1.72 Hz, Ph), 7.05 (1H, ddd, J = 8.04, 7.05, 0.32 Hz, Ph), 6.97 (1H, dd, J = 8.03, 0.32 Hz, Ph), 4.56 (2H, t, J = 6.46 Hz, OC$\underline{H}_2$CH$_2$), 2.82 (2H, t, J = 6.46 Hz, OCH$_2$C$\underline{H}_2$CO); ^{13}C NMR (100 MHz, $CDCl_3$) 191.86 (CO), 161.88, 136.02, 127.18, 121.41, 121.38, 117.91, 67.04 (O$\underline{C}$H$_2$), 37.82 (CH$_2\underline{C}$H$_2$CO): HRMS (EI, M$^+$) calcd for $C_9H_8O_2$ 148.0519; found 148.0520. *Data for 4-(phenylethynyl)-3,4-dihydro-2H-chromene* (**11a**). $[\alpha]_D^{20}$ −38 (*c* 1, Et_2O) ν_{max} (neat)/cm^{-1} 2976, 2846, 2060, 2031, 1610, 1600, 1501, 1457, 1230, 1120, 1070, 1021, 765; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (3H, m,Ph), 7.27-7.13 (3H, m, Ph), 7.07–7.00 (1H, m, Ph), 6.83–6.77 (1H, m, Ph), 6.75–6.72 (1H, m, Ph), 4.32–4.25 (1H, m, OCH$_2$), 4.14–4.06 (1H, m, OCH$_2$), 3.95 (1H, t, J = 6.18 Hz, CH), 2.26–2.04 (2H, m, CH$_2$): ^{13}C NMR (100 MHz, $CDCl_3$) 153.93, 131.74, 129.86, 128.45, 128.31, 128.04, 123.43, 121.88, 120.64, 117.07, 91.31, 82.21, 64.44, 29.16, 28.13: HRMS (EI, M$^+$) calcd for $C_{17}H_{14}O$ 234.1039; found 234.1044: HPLC (Chiralcel-OD-H column, hexane/IPA 10%, 254 nm): t_R = 8.58 (major), 16.73 min (minor).