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Synthesis of tetrahydropyran derivatives via a novel indium trichloride mediated cross-cyclization between epoxides and homoallyl alcohols

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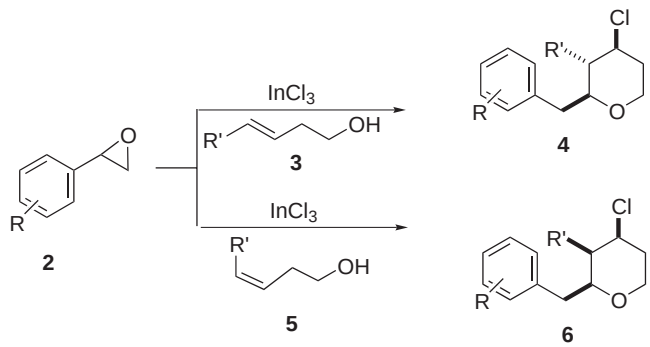
Abstract—A cross-cyclization between epoxides and homoallyl alcohols catalyzed by indium chloride generates tetrahydropyran derivatives in high yields.

Cytostatic macrolides apricularen A (**1a**) and B (**1b**) were recently isolated from culture extractions of *Chrondromyces robustus*.[1] Biological tests have shown that they are potential new antibiotics. A key structural feature of these natural products is the presence of a benzyl tetrahydropyran core. In an effort to provide such a benzyl tetrahydropyran derivative, as well as other related compounds,[2] we envisioned an effective method involving an in situ epoxide isomerization–cation olefin cyclization. Herein we wish to report a novel cross-cyclization between aryl-substituted vinyl epoxide and homoallyl alcohol mediated by indium chloride (Scheme 1).

Epoxides can be obtained readily from the epoxidation of corresponding olefins.[3] To begin our research, styrene epoxide was mixed with homoallyl alcohol in dry chloroform. The mixture was stirred with indium chloride[4] at room temperature. TLC showed that all the starting material had disappeared within 5 h. After a usual work-up, the crude product was separated by flash-column chromatography. ^{1}H NMR measurement



Scheme 1.

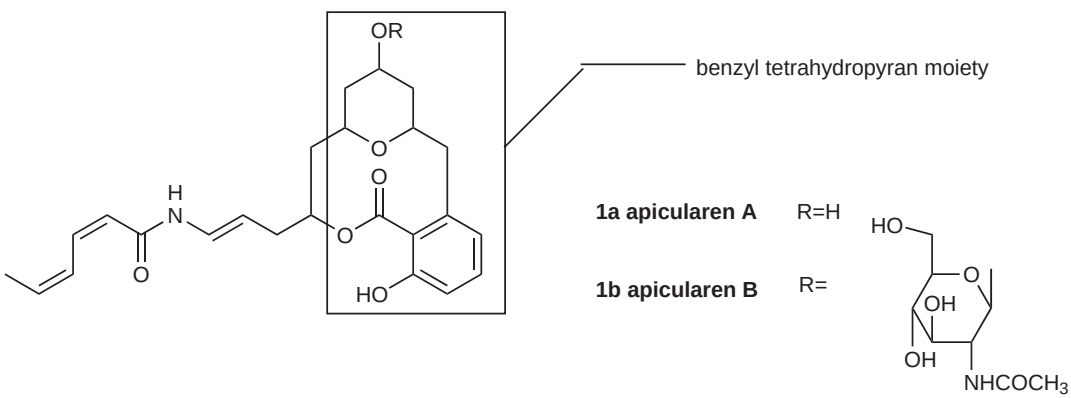


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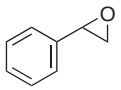
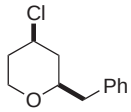
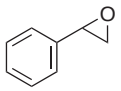
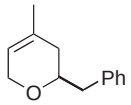
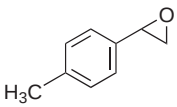
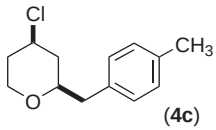
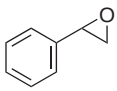
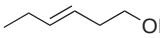
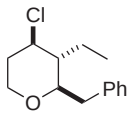
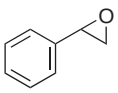
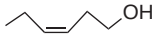
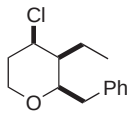
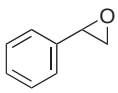
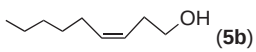
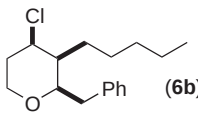
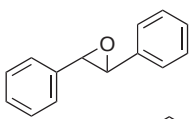
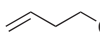
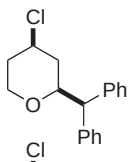
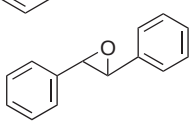
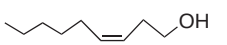
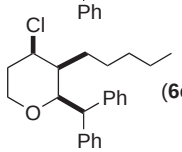
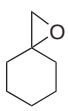
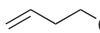
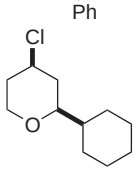
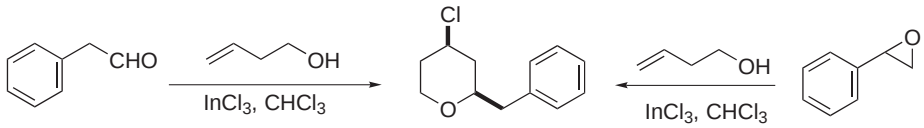
Table 1. Synthesis of tetrahydropyrans via cross-cyclization of homoallyl alcohol and epoxides

Entry	Epoxide	Alcohol	Products	Yield (%)
1		 (**3a**)	 (**4a**)	94 (*cis/trans*=3:1)
2		 (**3b**)	 (**4b**)	83
3		 (**3a**)	 (**4c**)	89
4		 (**3c**)	 (**4d**)	87
5		 (**5a**)	 (**6a**)	96
6		 (**5b**)	 (**6b**)	73
7		 (**3a**)	 (**4e**)	83 (*cis/trans*=4:1)
8		 (**5b**)	 (**6c**)	81
9		 (**3a**)	 (**4f**)	91 (*cis/trans*>10:1)

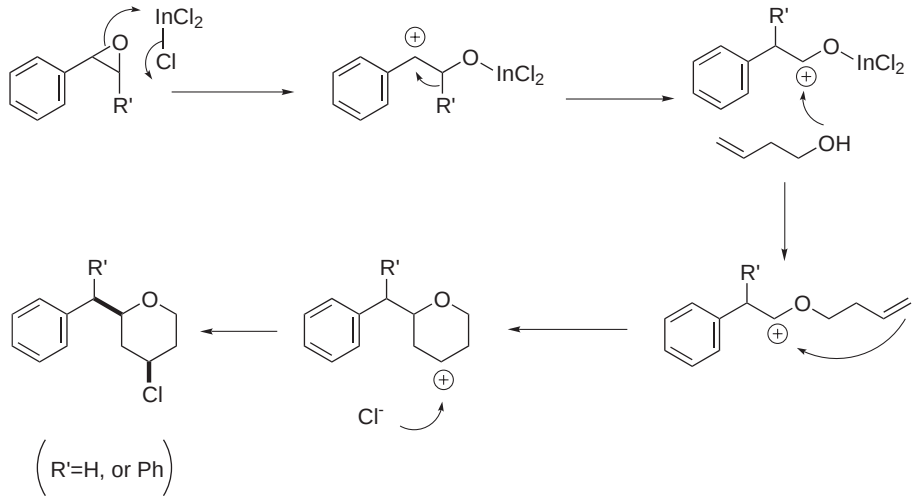
All experiments were carried out at room temperature for 5 h. Yields were isolated ones after column chromatography on silica gel. *Cis/trans* ratios were measured by ^{1}H NMR or GCMS; unless otherwise shown, negligible amounts of *trans* isomers were detected. The minor isomers of trisubstituted THP products were not isolated.

shows a clean formation of the benzyl tetrahydropyran derivative **4a**. Decoupling NMR, COSY and comparison with the NMR spectra of similar reported compounds showed the major product has a *cis* stereochemistry.[2]

Subsequently, various epoxides and unsaturated alcohols have been examined (Table 1). All of them provided high yields of the cyclization products, ranging from 70 to 90%. Interestingly, when *cis* unsaturated alcohols were used (entries 5, 6 and 8), 2,3,4-trisubstituted tetrahydropyrans with *cis* conformations were obtained as the major product.[5] However, when *trans* unsaturated alcohol (entry 4), such as *trans*-3-hexene-1-ol (**3c**), was used, 2,3,4-trisubstituted tetrahydropyran with a *trans–trans* conformation was obtained as the dominant product. It should be noted that in the case of stilbene oxide, the aromatic group migrates (entries 7 and 8), whereas in the case of styrene oxide, the hydrogen migrates. In addition, we have also carried out the tetrahydropyran formation by both the epoxide and the aldehyde methods. The same product was obtained by using the indium chloride mediated cross-cyclization between styrene epoxide and homoallyl alcohol, or the Prins-type cyclization between phenylacetaldehyde and homoallyl alcohol (Scheme 2).[6] A tentative mechanism to rationalize the product formation is shown in Scheme 3. As evidence to the proposed mechanism, an



Scheme 2.



Scheme 3. Proposed mechanism for the cross-cyclization of epoxides and homoallyl alcohols.

indium chloride-promoted rearrangement of epoxides was reported recently in which the epoxides were converted to aldehydes or ketones.[7]

A typical experimental procedure is as follows: 3-butene-1-ol (144 mg, 2 mmol), styrene oxide (360 mg, 3 mmol) and indium chloride (888 mg, 4 mmol) were stirred in dry chloroform (20 mL) at room temperature for about 5 h. After filtration, the solution was concentrated. The crude mixture was separated by flash-column chromatography (hexane/ethyl acetate = 30/1) on silica gel. Two isomers (3:1) of the desired product (total 398 mg, yield 94%) were obtained.[8]

Acknowledgements

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8. Characterization of products: **4a: (*cis*)** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.40–7.24 (m, 5H), 4.10–3.95 (m, 2H), 3.55 (m, 1H), 3.42 (dt, J = 2.0, 12.1 Hz, 1H), 3.0 (dd, J = 6.8, 13.8 Hz, 1H), 2.75 (dd, J = 6.5, 13.8 Hz, 1H), 2.15 (m, 2H), 1.92 (dt, J = 4.7, 12.0 Hz, 1H), 1.65 (q, J = 1.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 137.9, 129.4, 128.5, 126.5, 78.2, 67.1, 55.8, 42.5, 42.4, 37.1. Anal. calcd for $C_{12}H_{15}ClO$: C, 68.41; H, 7.18. Found: C, 67.97; H, 7.71. IR (neat, cm^{-1}): 3025, 2948, 2846, 1494, 1451, 762, 753, 691. **(*trans*)** ^{1}H NMR (400 MHz, $CDCl_3$, ppm): 7.3–7.2 (m, 5H), 4.58 (m, 1H), 4.09 (m, 1H), 3.95 (dt, J = 2.0, 11.7 Hz, 1H), 3.86 (dd, J = 5.0, 12.0 Hz, 1H), 2.90 (dd, J = 7.4, 13.8 Hz, 1H), 2.70 (dd, J = 5.9, 13.8 Hz, 1H), 2.1 (m, 1H), 2.0–1.75 (m, 3H). ^{13}C NMR (100 MHz,

$CDCl_3$, ppm): 138.12, 129.34, 128.28, 126.28, 72.21, 62.35, 56.35, 42.21, 39.02, 33.67. IR (neat, cm^{-1}): 2960, 2843, 1495, 1453, 1103, 1074, 764, 741.

4b: ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.3 (m, 5H), 5.45 (s, 1H), 4.21 (m, 2H), 3.7 (m, 1H), 3.04 (dd, $J=7.0$, 13.8 Hz), 2.80 (dd, $J=6.4$, 13.8 Hz, 1H), 2.06 (m, 1H), 1.8 (m, 1H), 1.7 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 138.6, 131.7, 129.4, 128.4, 126.3, 119.8, 74.7, 66.1, 42.5, 35.5, 23.1. MS: M = 189. IR (neat, cm^{-1}): 3029, 2935, 2869, 1679, 1490, 1448, 1132, 1075, 750, 698, 661.

4c: ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.35–7.15 (m, 4H), 4.12–3.88 (m, 2H), 3.5–3.28 (m, 2H), 2.75 (m, 1H), 2.05 (m, 1H), 1.85 (m, 2H), 1.6–1.4 (m, 2H), 1.4 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 138.9, 129.3, 128.2, 126.1, 80.6, 66.7, 60.5, 49.5, 39.5, 37.7, 20.7, 9.1. MS: M = 224. IR (neat, cm^{-1}): 3065, 3018, 2961, 2923, 2848, 1490, 1448, 763, 735, 698.

4d: ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.4–7.2 (m, 5H), 4.03 (dt, $J=4.7$, 10.6 Hz, 1H), 3.93 (ddd, $J=1.7$, 4.71, 12.1 Hz, 1H), 3.45 (dt, $J=2.4$, 9.6 Hz, 1H), 3.3 (dt, $J=2.0$, 12.0 Hz, 1H), 3.09 (dd, $J=2.3$, 14.3 Hz, 1H), 2.68 (dd, $J_1=9.1$, 14.3 Hz, 1H), 2.18–1.85 (m, 3H), 1.78–1.58 (m, 2H), 0.98 (t, $J=7.4$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 138.9, 129.3, 128.2, 126.1, 80.6, 66.7, 60.5, 49.5, 39.5, 37.7, 20.7, 9.1. IR (neat, cm^{-1}): 3027, 2932, 2866, 1490, 1452, 749, 698.

6a: ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.36–7.22 (m, 5H), 4.22 (dt, $J=4.4$, 11.4 Hz, 1H), 3.99 (ddd, $J=2.6$, 5.0, 11.8 Hz, 1H), 3.62 (ddd, $J=2.1$, 5.1, 9.1 Hz, 1H), 3.38 (dt, $J=2.9$, 14.4 Hz, 1H), 3.01 (dd, $J=9.1$, 14.1 Hz, 1H), 2.74 (dd, $J=4$, 14 Hz, 1H), 2.02 (m, 1H), 1.9–1.78 (m, 1H), 1.70 (m, 1H), 1.1 (t, $J=7.6$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 139.2, 129.1, 128.4, 126.2, 81.8, 66.3, 61.8, 47.3, 39.2, 32.5, 16.9, 15.6. Anal. calcd for $C_{14}H_{19}ClO$: C, 70.43; H, 8.02. Found: C, 70.91; H, 8.16. IR: (neat, cm^{-1}): 2957, 2839, 1492, 1453, 752, 680.

6b: ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.35–7.20 (m, 5H), 4.22 (dt, $J=4.4$, 11.8 Hz, 1H), 3.97 (ddd, $J=2.4$, 5.0, 11.6Hz, 1H), 3.6 (ddd, $J=2.0$, 4.1, 9.1 Hz, 1H), 3.38 (dt, $J=3.0$, 14.4 Hz, 1H), 3.0 (dd, $J=8.9$, 14.4 Hz, 1H), 2.72 (dd, $J=4.1$, 14.1 Hz, 1H), 2.02 (m, 1H), 1.85 (m, 2H), 1.3–1.75 (m, 9H), 0.95 (t, $J=7.0$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 139.2, 129.7, 128.3, 126.2, 81.9, 66.5, 61.9, 45.6, 39.3, 32.5, 32.2, 30.8, 23.9, 22.5, 14.0. Anal. calcd for $C_{17}H_{25}ClO$: C, 72.71; H, 8.97. Found: C, 72.93; H, 9.19. IR (neat, cm^{-1}): 3022, 2932, 2857, 1491, 1456, 738, 695.

4e: (*cis*) ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.36–7.20 (m, 10H), 4.10–3.95 (m, 4H), 3.46 (dt, $J=2.0$, 8.4 Hz, 1H), 2.21–2.0 (m, 2H), 1.90 (m, 1H), 1.61 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 141.8, 141.7, 128.6, 128.6, 128.4, 128.3, 126.7, 126.4, 78.9, 67.2, 57.4, 56.1, 41.5, 36.9. MS: M = 286. IR (neat, cm^{-1}): 3021, 2956, 2852, 1596, 1492, 1445, 746, 695. **(*trans*)** ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.31–7.08 (m, 10H), 4.52 (dt, $J=8.0$ Hz, 1H), 4.53 (s, 1H), 3.92 (t, $J=12.0$ Hz, 1H), 3.80 (m, 2H), 1.98 (m, 1H), 1.70 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 142.1, 124.0, 128.6, 128.4, 128.3, 126.5, 126.3, 73.3, 62.5, 57.1, 56.6, 38.2, 33.6. MS: M = 286. Anal. calcd for $C_{18}H_{19}ClO$: C, 75.38; H, 6.68. Found: C, 75.62; H, 7.09. IR (neat, cm^{-1}): 3085, 3059, 2961, 2805, 1594, 1491, 750, 698.

6c: ^1H NMR (400 MHz, $CDCl_3$, ppm): 7.32–7.13 (m, 10H), 4.26 (dt, $J=4.1$, 12.7 Hz, 1H), 4.1 (q, $J=11.2$, 20.0 Hz, 1H), 3.93 (dd, $J=4.7$, 12.1 Hz, 1H), 3.40 (dt, $J=2.6$, 12.0 Hz, 1H), 2.06 (m, 1H), 1.84 (m, 2H), 1.67 (m, 1H), 1.48 (m, 1H), 1.25 (m, 5H), 1.0 (m, 5H), 1.0 (m, 1H), 0.86 (t, $J=6.8$ Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 142.9, 141.2, 128.8, 128.4, 128.3, 127.8, 126.8, 126.3, 83.1, 68.1, 62.3, 54.2, 42.8, 32.3, 32.1, 30.4, 23.5, 22.4, 14.1. IR (neat, cm^{-1}): 2959, 2840, 1495, 1453, 1104, 1071, 764, 740, 690.

4f: ^1H NMR (400 MHz, $CDCl_3$, ppm): 4.05 (m, 2H), 3.38 (dt, $J=2.1$, 12.0 Hz, 1H), 3.03 (m, 1H), 2.15 (m, 1H), 2.08 (m, 1H), 1.85 (m, 2H), 1.7 (m, 4H), 1.6 (m, 1H), 1.4 (m, 1H), 1.3–0.9 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): 87.7, 67.1, 56.7, 42.8, 39.9, 37.3, 28.9, 28.6, 26.5, 26.2, 26.1. MS: M = 202. IR (neat, cm^{-1}): 2954, 2859, 1449, 1340, 1250, 1156, 1000, 759.