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# Concise syntheses of (+)- and (−)-methylenolactocins and phaseolinic acids

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**Abstract**

(+)- and (−)-Methylenolactocins and phaseolinic acids are synthesized in four steps via asymmetric *syn*- and *anti*-aldol reactions of chiral *N*-succinyl-2-oxazolidinones using the same set of reagents.


Paraconic acids are a class of naturally occurring trisubstituted γ-butyrolactones containing a C4-carboxylic acid group.[1] They have a similar substitution pattern at the C3-position bearing either a methyl or a methylene group. Differences in the alkyl substituents at C5 position and in the stereochemical relationship among the substituents lead to a number of paraconic acids in Nature. In addition, some of the paraconic acids are isolated in both (+)- and (−)-forms. So, structurally they can be grouped as (i) 4,5-*trans*-paraconic acids such as methylenolactocin **1**, protolichesterinic acid **2**, nephrosterinic acid **3**, and roccellaric acid **4**; and (ii) 4,5-*cis*-paraconic acids, for example, phaseolinic acid **5** and nephromopsinic acid **6** (Fig. 1). In view of their important biological activities, such as antifungal, antitumor, and antibacterial, the syntheses of these lactones have attracted considerable interest from organic and medicinal chemists. There are a number of racemic as well as asymmetric syntheses of *individual* paraconic acids.[2–4] However, common asymmetric methods for the synthesis of both the 4,5-*cis*- and *trans*-paraconic acids are few in the literature.[5] Development of a general strategy for the synthesis of both the paraconic acids in their (+)- and (−)-forms is still a challenging task to organic chemists. Herein, we report a general approach for the synthesis of (+)- and (−)-4,5-*trans*- and *cis*-paraconic acids, for example (+)- and (−)-methylenolactocins (4,5-*trans*) and phaseolenic acids (4,5-*cis*) has been demonstrated.

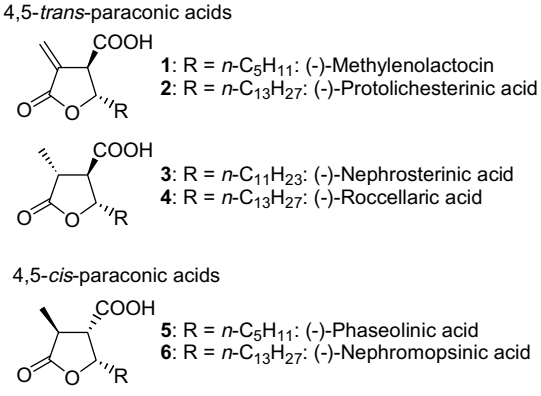


Fig. 1.

Recently, we reported[6] asymmetric *syn*- and *anti*-aldol reactions[7] using the same set of reactants and reagents by simply inverting the sequence of base and aldehyde additions, using *N*-acyl oxazolidinones containing a γ/δ-oxygen functionality (Scheme 1). Accordingly, the synthesis of (+)- and (−)-methylenolactocins **1** and phaseolinic acids **5** was initiated from *N*-succinyl-2-oxazolidinones **7** and **8**

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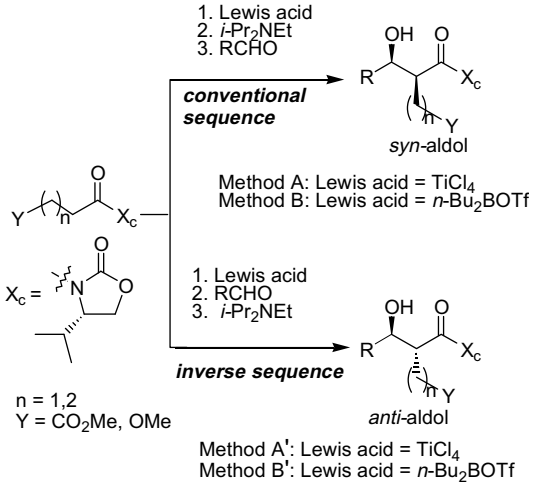
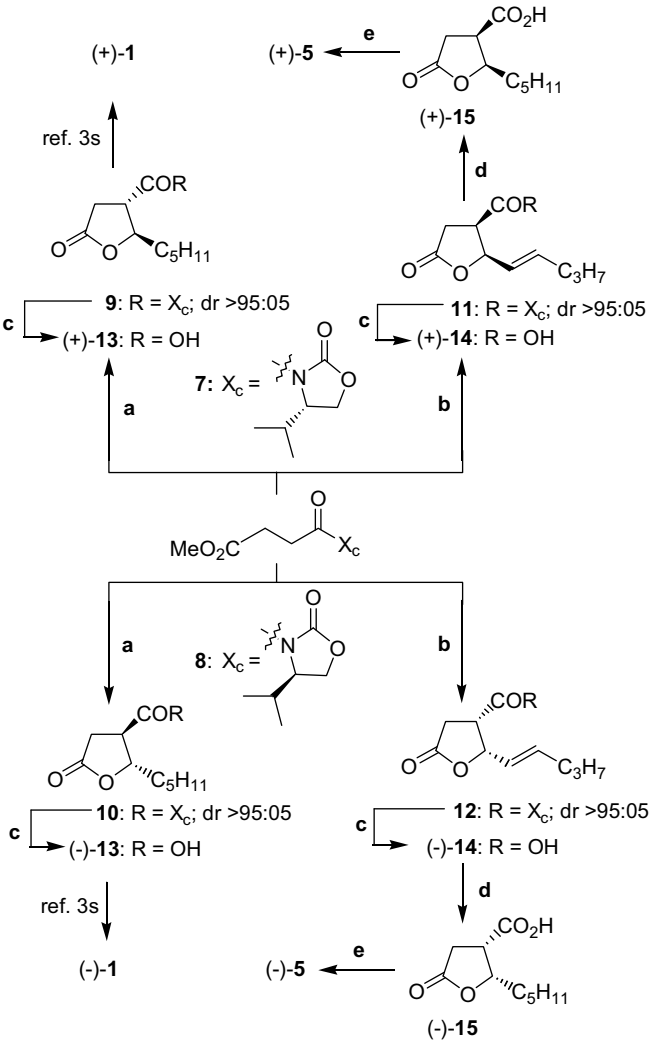



Scheme 1.

(Scheme 2). *syn*-Aldol reactions of **7** and **8** with *n*-hexanal under conventional conditions (Method A: $TiCl_4$, *i*-$Pr_2NEt$ followed by aldehyde −78 to −15 °C or Method B: *n*-$Bu_2OTf$ instead of $TiCl_4$) and in situ lactonization afforded the *trans*-lactones **9** and **10** in high diastereoselectivity (dr >95:05) with good yields. Under the inverse methods (Method A′: $TiCl_4$, aldehyde followed by *i*-$Pr_2NEt$ −78 to −15 °C or Method B′: *n*-$Bu_2OTf$ instead of $TiCl_4$), *anti*-aldol reactions of **7** and **8** with 2-hexenal provided, respectively, *cis*-lactones **11** and **12** (dr >95:05 ). The selective removal of the chiral auxiliaries of lactones **9**–**12** by treatment with LiOH, $H_2O_2$ in THF at 0 °C provided lactones (+)-**13**, (−)-**13**, (+)-**14**, and (−)-**14** in high yields.[8,9] Catalytic hydrogenation of **14** provided lactones (+)-**15** and (−)-**15**, which are isomeric with lactones **13** having the desired carboxyl and pentyl substituents at the C4 and C5 positions, respectively. The introduction of a methylene substituent at C3 of **13** to afford (+)- and (−)-methylenolactocins **1** has already been reported.[3s]

C3-Methylation of **15** with NaHMDS and MeI afforded (+)- and (−)-phaseolinic acids **5** in 77% and 75% yields (over two steps), respectively. The identity and optical purity of synthetic (+)- and (−)-phaseolinic acids **5** were confirmed by comparison with the spectral and physical properties of those reported in the literature {(+)-**5**: $[\alpha]_D^{29}$ +114.04 (*c* 0.50, $CHCl_3$); (−)-**5**: $[\alpha]_D^{29}$ −113.95 (*c* 0.50, $CHCl_3$); [lit.[4a] $[\alpha]_D$ −114.4 (*c* 1.46, $CHCl_3$)]}.[10] Similarly, asymmetric *syn*- and *anti*-aldol reactions of succinyl substrates **7** and **8** with tetradecanal and 2-tetradecenal followed by similar chemical modifications could provide (+)- and (−)-roccellaric acids, protolichesterinic acids, and nephromopsinic acids.

In conclusion, we have developed a common strategy for the enantioselective synthesis of 4,5-*trans*- and *cis*-paraconic acids in their (+)- and (−)-forms. This was demonstrated by the synthesis of (+)- and (−)-methylenolactocins (4,5-*trans*) and phaseolinic acids (4,5-*cis*) from the common reactants and reagents.




Scheme 2. Reagents and conditions: (a) Method A: $TiCl_4$ (1.1 equiv), *i*-$Pr_2NEt$ (1.2 equiv), *n*-hexanal (1.5 equiv), −78 °C, 2 h, −15 °C, 20 h, 64% (**9**), 62% (**10**) or Method B: *n*-$Bu_2OTf$ (1.1 equiv) instead of $TiCl_4$ otherwise the same as Method A, 75% ( **9**), 80% (**10**); (b) Method A′: $TiCl_4$ (1.2 equiv), 2-hexenal (1.5 equiv), *i*-$Pr_2NEt$ (1.4 equiv), −78 °C, 3 h, then −15 °C, 20 h, 72% (**11**), 70% (**12**) or Method B′: *n*-$Bu_2BOTf$ (2.5 equiv), 2-hexenal (1.4 equiv), *i*-$Pr_2NEt$ (2.5 equiv), otherwise the same as Method A′, 81% (**11**), 78% (**12**); (c) LiOH, $H_2O_2$, THF–$H_2O$ (3:1), 0 °C, 3.5 h, 95–97%; (d) 10% Pd/C, $H_2$ (1 atm), MeOH, 25 °C, quantitative yields, (e) NaHMDS (2.2 equiv), $CH_3I$ (5.0 equiv), THF, −78 °C to −20 °C, 3 h; 75% [(−)- **5**, over two steps], 77% [(+)-**5**, over two steps].

## Acknowledgments

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8. *(2S,3R)-5-oxo-2-pentyl-tetrahydrofuran-3-carboxylic acid* [(−)-**13**]: A white solid; mp 103–105 °C, (lit.[3k] mp 105–107 °C); $[\alpha]_D^{29}$ −54.19 (*c* 0.52, $CHCl_3$), [lit.[3s] $[\alpha]_D^{21}$ −54.0 (*c* 0.50, $CHCl_3$)]; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 4.61 (q, $J = 5.3$ Hz, 1H), 3.20–3.00 (m, 1H), 3.00–2.65 (m, 2H), 1.90–1.65 (m, 2H), 1.60–1.15 (m, 6H), 1.00–0.75 (m, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 175.3, 173.6, 82.2, 48.6, 34.8, 31.7, 30.9, 24.5, 22.0, 13.5. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.81; H, 8.23.
*(2R,3S)-5-oxo-2-pentyl-tetrahydrofuran-3-carboxylic acid* [(+)-**13**]: A white solid; mp 104–105 °C, $[\alpha]_D^{29}$ +54.08 (*c* 0.51, $CHCl_3$); spectroscopic data ($^1H$ NMR, $^{13}C$ NMR) are identical with (−)- **13**; Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.53; H, 8.27.
9. *(2S,3S)-5-oxo-2-(1E-pentenyl) tetrahydrofuran-3-carboxylic acid* [(−)-**14**]: A gummy liquid, $[\alpha]_D^{29}$ −31.28 (*c* 0.51, $CHCl_3$); $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 5.89 (dt, $J = 15.2$, 6.6 Hz, 1H), 5.45 (dd, $J = 15.2$, 7.6 Hz, 1H), 5.14 (t, $J = 7.6$ Hz, 1H), 3.56 (q, $J = 7.6$ Hz, 1H), 2.97 (dd, $J = 17.6$, 7.2 Hz, 1H), 2.68 (dd, $J = 17.6$, 8.7, 1H), 2.06 (q, $J = 6.7$ Hz, 2H), 1.55–1.15 (m, 2H), 0.88 (t, $J = 8.0$ Hz, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 175.8, 172.7, 137.6, 122.8, 80.6, 44.9, 33.9, 31.0, 21.6, 13.2. Anal. Calcd for ($C_{10}H_{16}O_4 + 0.25H_2O$): C, 59.25; H, 7.21. Found: C, 59.28; H, 7.64.
*(2S, 3S)-5-oxo-2-(1E-pentenyl)-tetrahydrofuran-3-carboxylic acid* [(+)-**14**]: $[\alpha]_D^{29}$ +31.28 (*c* 0.51, $CHCl_3$). Spectroscopic data ($^1H$ NMR, $^{13}C$ NMR) are identical with (−)-**14**.
10. *(2S,3S,4S)-4-Methyl-5-oxo-2-pentyl-tetrahydrofuran-3-carboxylic acid [(−)-Phaseolinic acid]* [(−)-**5**]: A white solid; mp = 138–140 °C (lit.[1b,4a] mp = 136–137 °C), $[\alpha]_D^{29}$ −113.95 (*c* 0.50, $CHCl_3$), [lit.[1b,4a] $[\alpha]_D$ −114.4 (*c* 1.46, $CHCl_3$)]; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 4.65 (dt, $J = 8.3$, 5.4 Hz, 1H), 3.24 (dd, $J = 9.7$, 8.4 Hz, 1H), 3.15–2.95 (m, 1H), 1.60–1.50 (m, 2H), 1.50–1.30 (m, 2H), 1.30–1.20 (m, 4H), 1.31 (d, $J = 7.0$ Hz, 3H), 0.88 (t, $J = 7.0$ Hz, 3H). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 177.3, 175.0, 77.6, 51.4, 36.3, 31.4, 31.1, 25.3, 22.6, 14.5, 13.8. Anal. Calcd for ($C_{11}H_{18}O_4 + 0.33H_2O$): C, 59.98; H, 8.54. Found: C, 59.75; H, 8.30.
*(2R,3R,4R)-4-Methyl-5-oxo-2-pentyl-tetrahydrofuran-3-carboxylic acid* [(+)-**5**]: (+)-phaseolinic acid. ($^1H$ NMR, $^{13}C$ NMR) are identical with (−)-phaseolinic acid (−)-5. $[\alpha]_D^{29}$ +114.04 (*c* 0.50, $CHCl_3$).