A Concise Synthesis of (-)-Methylenolactocin and (-)- Phaseolinic Acid from (6*S*,9*S*)-Tetradec-7-yne-6,9-diol

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Abstract: A novel, stereodivergent route to paraconic acids from C_2-symmetric *trans*- and *cis*-alk-2-ene-1,4-diols through Ireland-Claisen and/or Johnson orthoester rearrangements is disclosed. This strategy has been applied to the synthesis of (-)-methylenolactocin and (-)-phaseolinic acid from a single chiral diol.

Key words: rearrangements, lactones, stereoselective synthesis, reductions

Paraconic acids are biologically active γ-butyrolactones isolated from various species of mosses, lichens, and fungi,[1] which possess a very similar substitution pattern at the α-position (methyl or methylene group) and β-position (carboxyl group). However, they differ in the residue attached to the γ-position as well as in the stereochemical relationship between these substituents. Representative examples are the antitumoral antibiotic (-)-methylenolactocin,[2] **1**, and (-)-phaseolinic acid,[3] **2**.

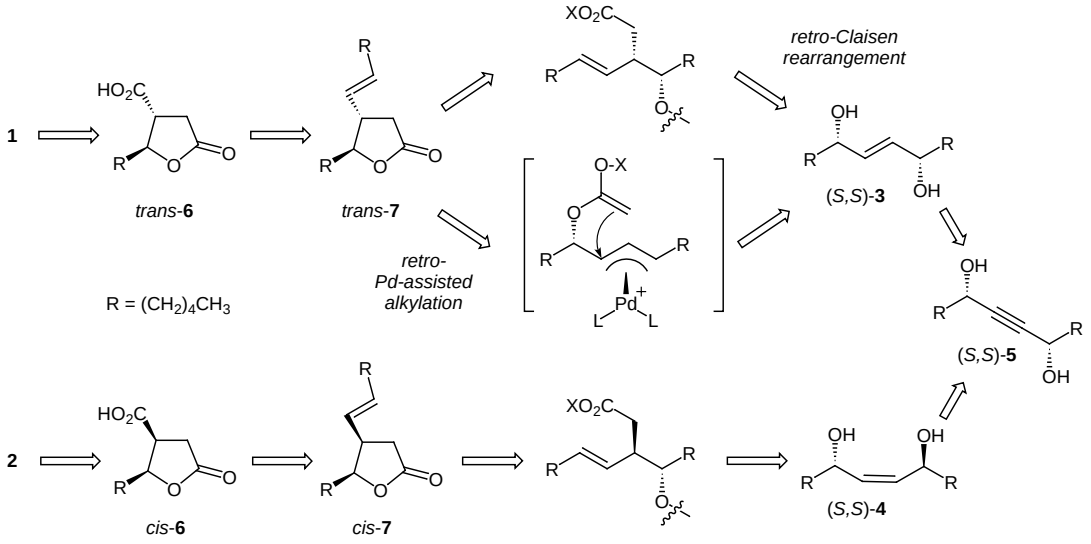
1 **2**

Figure 1

Due to their biological significance, the preparation of such lactones has attracted growing attention. Thus, several efficient enantioselective syntheses of β,γ-*trans* compounds of this class (e.g. **1**) have been reported recently[4] but β,γ-*cis* disubstituted systems (as in **2**) seem to be more difficult to obtain.[5]

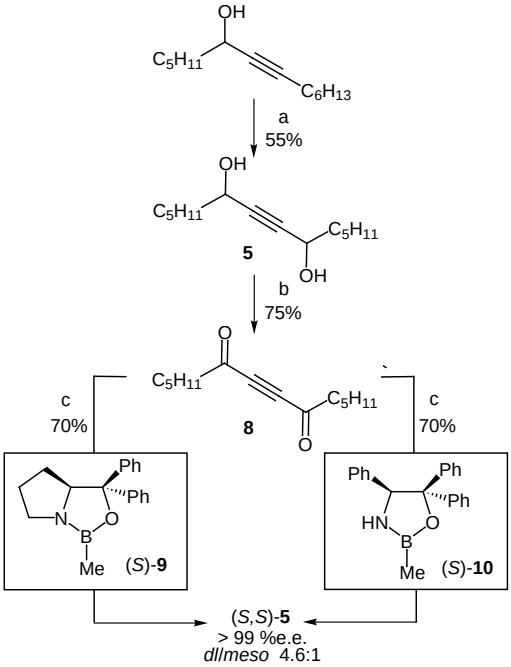
We have recently described a route to chiral unsaturated 1,4-diols through the oxazaborolidine-mediated reduction of the parent ethylenic or acetylenic diketones.[6] These C_2-symmetric unsaturated diols, **3**-**5**, may be a versatile gateway to several natural products, including β,γ-*trans* and β,γ-*cis* series of paraconic acids. Thus, according to our retrosynthetic analysis outlined in Scheme 1, lactone *trans*-**6** would arise from (*S*,*S*)-**3** through a Claisen-like rearrangement (or a Pd-assisted intramolecular alkylation) followed by oxidation of the double bond, while the *cis*-**6** would come from (*S*,*S*)-**4**. Since efficient transformations of acids *trans*- and *cis*-**6** into **1** and **2**, respectively, have been previously described,[4k,5b] this approach would constitute a formal synthesis of (-)-methylenolactocin (**1**) and of (-)-phaseolinic acid (**2**) from a single chiral diol, (*S*,*S*)-**5**. We wish to report here our findings in this connection.

The required diol (*S*,*S*)-**5** was obtained as shown in Scheme 2. Addition of hexanal to a premixed solution of oct-1-yne and BuLi gave crude tetradec-7-yn-6-ol (94%) which was first treated with *t*-BuOOH/SeO_2 according to



Scheme 1

a Sharpless procedure[7] to give tetradec-7-yne-6,9-diol[8] (**5**, mixture of stereoisomers), and then transformed into diketone **8** by the Jones oxidation. Stereoselective reduction was successfully accomplished by using oxazaborolidines (*S*)-**9** (CBS reduction)[9] or (*S*)-**10**[6] to afford (*S,S*)-**5** (70%, >99% e.e.)[10] along with with *meso*-**5**. Fortunately, after reduction of the triple bond to olefin **3** (90%, $LiAlH_4$, THF, Δ) or **4** (75%, H_2, Lindlar catalyst, EtOAc), the undesired *meso* isomers could be readily removed by flash chromatography.

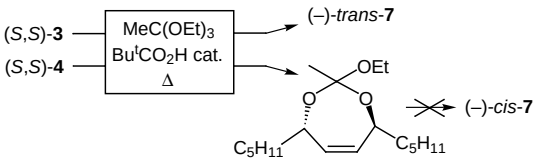


a) (i) *t*-BuOOH, SeO_2, CH_2Cl_2, r.t. 24 h; (ii) $NaBH_4$, MeOH, 0 °C; b) CrO_3, aq. H_2SO_4, 0 °C; c) BMS (2 mmol), (*S*)-**9** or (*S*)-**10** (0.4 mmol), slow addition of **8** (1 mmol), THF, 0 °C.

Scheme 2

Having in hand enantiopure (*S,S*)-**3** and (*S,S*)-**4**, our efforts were first focused on the study of their Johnson orthoester rearrangement (Scheme 3).[11a] To our satisfaction, we found that by refluxing (*S,S*)-**3** in $CH_3C(OEt)_3$ with a catalytic amount of pivaloic acid, the lactone *trans*-**7** was isolated in 50% yield in a single step with complete stereoselectivity. In this connection, it is noteworthy that the same conditions when applied to (*S,R*)-**3** led to racemic *cis*-**7**. However, a similar treatment of (*S,S*)-**4** gave mainly the cyclic orthoester. It should be noted that previous monoprotection (acetyl or *tert*-butyldimethylsilyl groups) of diols **3** and **4** did not improve the overall yields of lactone.

Looking for a clean access to both *cis* and *trans* lactones **7**, we examined the Pd-assisted intramolecular alkylation (see Scheme 1) of diacetates **11** and **12** derived from diols **3** and **4**, respectively (Figure 2). Unfortunately, attempts from several monoenolates (Li,[12] B,[13] Sn,[14] or Si[14]) of **11** or **12** under different Pd(0) conditions failed to give the desired lactones.



Scheme 3

Then, we turned our attention to the Ireland-Claisen rearrangement[11] of the *tert*-butyldimethylsilyl enolates derived from diacetates **11** and **12**. When we treated (*S,S*)-**11** with an excess of *t*-$BuMe_2SiCl$ and potassium bis(trimethylsilyl)amide (KHMDS) in THF at -78 °C and then heated the mixture in refluxing toluene we isolated the acid *threo*-**13a** (44%) besides its *tert*-butyldimethylsilyl ester (*threo*-**13b**, 44%). A similar behaviour was noted for diacetate **12** to give *erythro*-**13**. It should be pointed out that, as expected, the configuration of the starting olefin determines the emergent C(3) configuration.

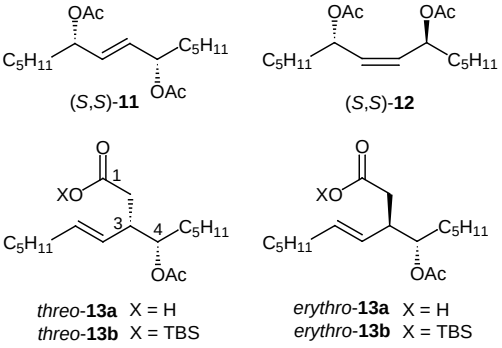
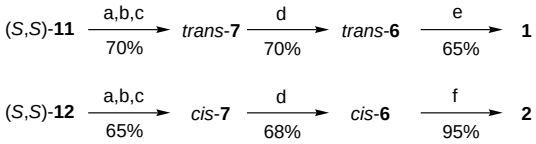


Figure 2



a) KHMDS, *t*-$BuMe_2SiCl$, THF, -78 °C Æ r.t., then anhyd toluene, Δ; b) LiOH, H_2O/THF,Δ; c) aq HCl/THF,Δ; d) cat. $RuCl_3$, $NaIO_4$, CCl_4/MeCN/H_2O 2:2:3; e) Ref. 4k; f) Ref. 5b.

Scheme 4

Since basic hydrolysis (LiOH, refluxing 1:1 THF/H_2O) of both *threo*-**13a** and *threo*-**13b** separately, followed by acidic treatment led to *trans*-**7**, we attempted the direct transformation of (*S,S*)-**11** into *trans*-**7** without isolation of any intermediate. We were gratified to obtain a 70% overall yield of *trans*-**7**[15] in such a transformation, as outlined in Scheme 4. In a similar way, (*S,S*)-**12** was converted into lactone *cis*-**7**. Eventually, lactones **6**[16] were readily obtained by $RuCl_3/NaIO_4$ oxidation[17] of compounds **7** (Scheme 4).

In summary, the formal syntheses of (-)-methylenolactocin (**1**) and of (-)-phaseolinic acid (**2**) disclosed herein, ex-

emplify the usefulness of C_2-symmetric *trans*- and *cis*-2-alkene-1,4-diols as precursors of β,γ-*trans* and β,γ-*cis* paraconic acids. Extension of this methodology to α-methylated paraconic acids by Claisen-type rearrangements of propionyl derivatives is under investigation.

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(10) The observed stereoselectivity depends on the amount of catalyst used. For instance: *i*) 2 equiv. of **9**, >99% e.e., *dl/meso* = 12:1; *ii*) 1.0 equiv. of **9**, >99% e.e., *dl/meso* = 5.7:1; *iii*) 0.2 equiv. of **9**, 99% e.e., *dl/meso* = 2.8:1.

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(15) **Preparation of (4*S*,5*S*)-4-[*(E)*-Hept-1-enyl)]-5-pentyl-4,5-dihydro-(3*H*)-furan-2-one (*trans*-7):** To a solution of (*S*,*S*)-**11** (120 mg, 0.38 mmol) and *t*-$BuMe_2SiCl$ (239 mg, 1.53 mmol) in anhyd THF (4 mL) at −78 °C under argon, a toluene solution of KHMDS (0.5 M, 2.30 mL, 1.15 mmol) was added dropwise, and the mixture was stirred at r.t. overnight. Then, most of the solvent was removed under vacuum, anhyd toluene (8 mL) was added and the mixture was heated (130 °C bath temperature) for 10 h. The reaction mixture was partitioned by adding diethyl ether (50 mL) and brine (10 mL). The aqueous layer was washed with additional diethyl ether (10 mL) and the organic layers were dried ($MgSO_4$), and concentrated in vacuo. The residue was filtered through a pad of silica gel and the mixture of the acid *threo*-**13a** and its silyl ester (*threo*-**13b**) was treated with THF (2 mL) and aq LiOH (8 M, 1 mL) at 70 °C for 9 h. The solution was then acidified with aq HCl (2 M, 6 mL), additional THF (3 mL) was added and the mixture was heated al 50 °C for 6 h. The mixture was partitioned by adding CH_2Cl_2 (50 mL), and the organic layer was dried ($MgSO_4$). Evaporation of solvents and purification by flash chromatography on silica gel gave (95: 5 hexane/EtOAc) *trans*-**7** as a yellowish oil (68 mg, 70% overall yield).
Data for **(4*S*,5*S*)-4-[*(E)*-hept-1-enyl)]-5-pentyl-4,5-dihydro-(3*H*)-furan-2-one (*trans*-7):** R_f 0.73 (65:35 hexane/EtOAc); $[\alpha]_D^{20}$ −52.9 (*c* = 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90 (t, 6H, *J* = 7.0 Hz, CH_3CH_2), 1.27−1.65 (m, 14H, CH_2), 1.95−2.05 (m, 2H, CH_2CH=CH), 2.41 (dd, 1H, *J* = 16.5, 10.0 Hz, HCH'CO_2), 2.60−2.80 (m, 2H, HCH'CO_2 and CHCH=CH), 4.10 (td, 1H, *J* = 8.2, 3.4 Hz, CHO), 5.25 (dd, 1H, *J* = 15.3, 8.7 Hz, CH_2CH=CH), 5.55 (dt, 1H, *J* = 15.3, 6.9 Hz, CH_2CH=CH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 13.8 ($CH_3(CH_2)_4$), 13.9 ($CH_3(CH_2)_4$), 22.4, 25.4, 28.7, 30.8, 31,2, 31.4, 32.3, 33.4 and 36.0 (CH_2), 45.5 (CHCH CH), 85.3 (CHO), 127.3 (CH = $CHCH_2$), 134.3 (CH=$CHCH_2$), 176.0 (C=O); IR (film) 2930, 1785, 1466, 1204; HRMS (M^+) calcd for $C_{16}H_{28}O_2$:252.2089, found 252.2080.
Data for **(4*R*,5*S*)-4-[*(E)*-Hept-1-enyl)]-5-pentyl-4,5-dihydro-(3*H*)-furan-2-one (*cis*-7) :** Yellowish oil; R_f 0.35 (9:1 hexane/EtOAc); $[\alpha]_D^{20}$ −37.7 (*c* = 0.53, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, 6H, *J* = 6.9 Hz, CH_3CH_2), 1.27−1.57 (m, 14H, CH_2), 1.98−2.08 (m, 2H, CH_2CH=CH), 2.38 (dd, 1H, *J* = 17.4, 5.5 Hz, HCH'CO_2), 2.68 (dd,1H, *J* = 17.4, 7.9 Hz, HCH'CO_2), 3.04−3.14 (m, 1H, CHCH=CH), 4.42−4.50 (m, 1H, CHO), 5.33 (dd, 1H, *J* = 15.6, 8.7 Hz, CH_2CH=CH), 5.54 (td, 1H, *J* = 15.6, 6.6 Hz, CH_2CH=CH); ^{13}C NMR ($CDCl_3$, 75.4 MHz) δ 14.0 ($CH_3(CH_2)_4$), 14.1 ($CH_3(CH_2)_4$), 22.5, 25.3, 28.8, 30.8, 31,3, 31.6, 32.4, 33.4 and 35.4 (CH_2), 42.3 (CHCH=CH), 83.7 (CHO), 125.4 (CH=$CHCH_2$), 134.4 (CH=$CHCH_2$), 176.6 (C=O); IR (film) 2940, 1780, 1458, 1210; HRMS (M^+) calcd for $C_{16}H_{28}O_2$:252.2089, found 252.2096.

(16) Spectral data of *cis*- and *trans*-**6** fully agree with those reported in ref. 5c and 4g.

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