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Enantiodivergent Synthesis of Both Enantiomeric Forms of Substituted Paraconic Acids Starting from D-Mannitol as a Chiral Pool

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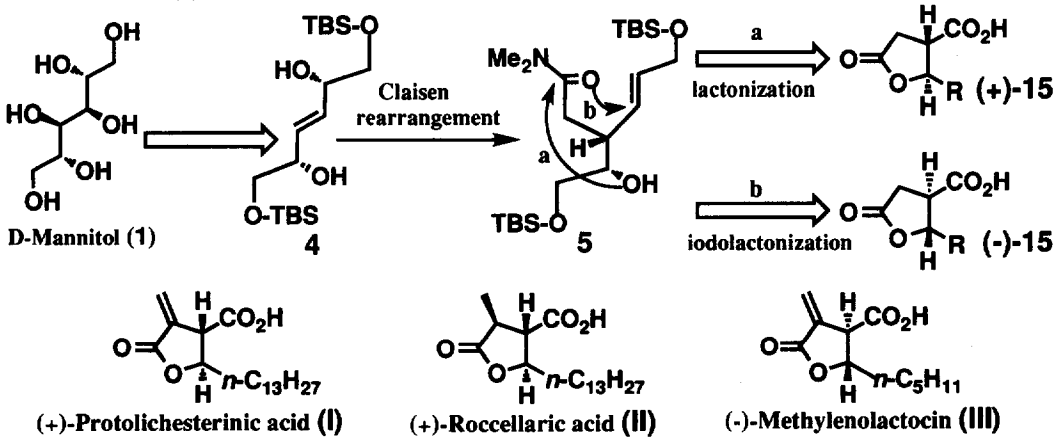
Abstract: Acetamide-acetal Claisen rearrangement of the C_2-symmetric enediol easily derived from D-mannitol provided a chiral C8-building block, which was demonstrated to be versatile for divergent synthesis of both enantiomeric forms of substituted paraconic acids.

Among the methods for producing chiral compounds, much efforts have been devoted to the method utilizing easily available chiral pools due to the reliability on the stereogenic centers.[1] D-Mannitol (**1**) has been widely used as an inexpensive hexitol chiral pool with four asymmetric carbons[2a] and mainly served as a convenient supplier for chiral glyceraldehyde[2b] and unnatural tartrate building blocks[2c] through glycol cleavage at the central and both terminal positions of protected D-mannitol (**1**), respectively. We have intended to make new versatile chiral building blocks by facile derivation of D-mannitol (**1**). In this paper, we report a facile preparation of a branched chiral C8-building block (**5**) from D-mannitol (**1**) and its use for formal total syntheses of optically active substituted paraconic acids, (+)-protolichesterinic acid (**I**),[3a] (+)-roccellaric acid (**II**),[3b] and (-)-methylenolactocin (**III**).[3c] The synthesis described features acetamide-acetal Claisen rearrangement[4] of the C_2-symmetric enediol (**4**), easily derived from D-mannitol (**1**), leading to a chiral C8-building block (**5**) and divergent transformation of the amide (**5**) to both enantiomeric forms ((+)- and (-)-**15**) of the key intermediates for synthesis of optically active substituted paraconic acids (**I**, **II**, **III**) via (a) lactonization and (b) iodolactonization.



(2*S*,5*S*)-1,2:5,6-Di-*O*-isopropylidene-3*E*-hexene (**2**) prepared in 41% overall yield from D-mannitol (**1**) according to the literatures[5] were converted into the 1,6-*O*-di-*tert*-butyldimethylsilyl (TBS) ether (**4**) via 3*E*-hexene-1,2,5,6-tetraol (**3**) in 70% yield through 2 steps. Although orthoester-Claisen rearrangement using

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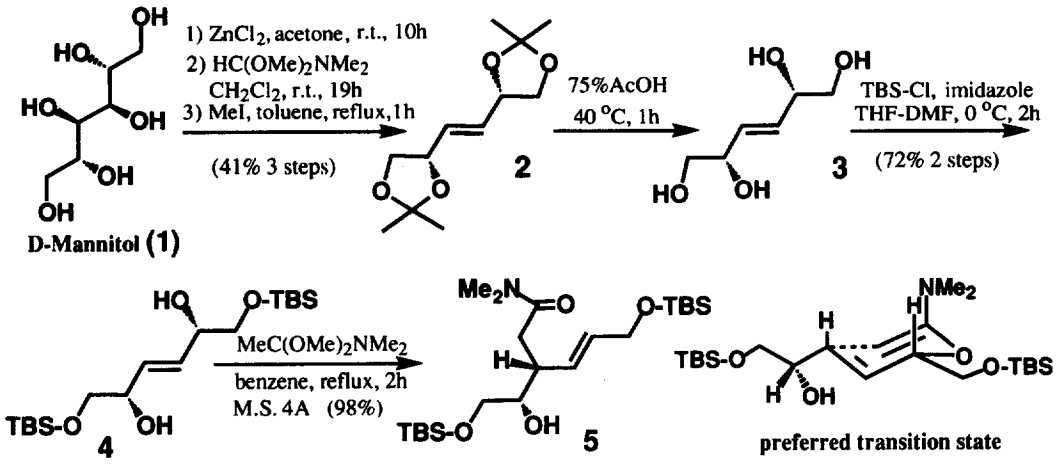
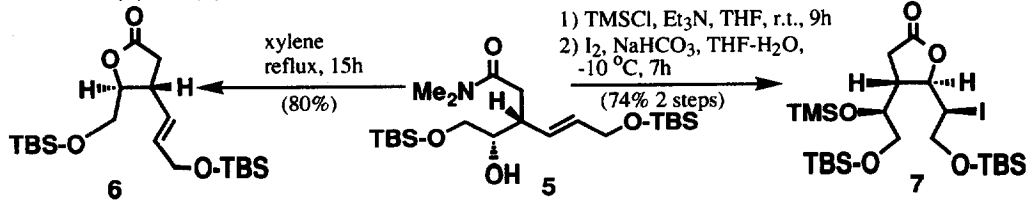
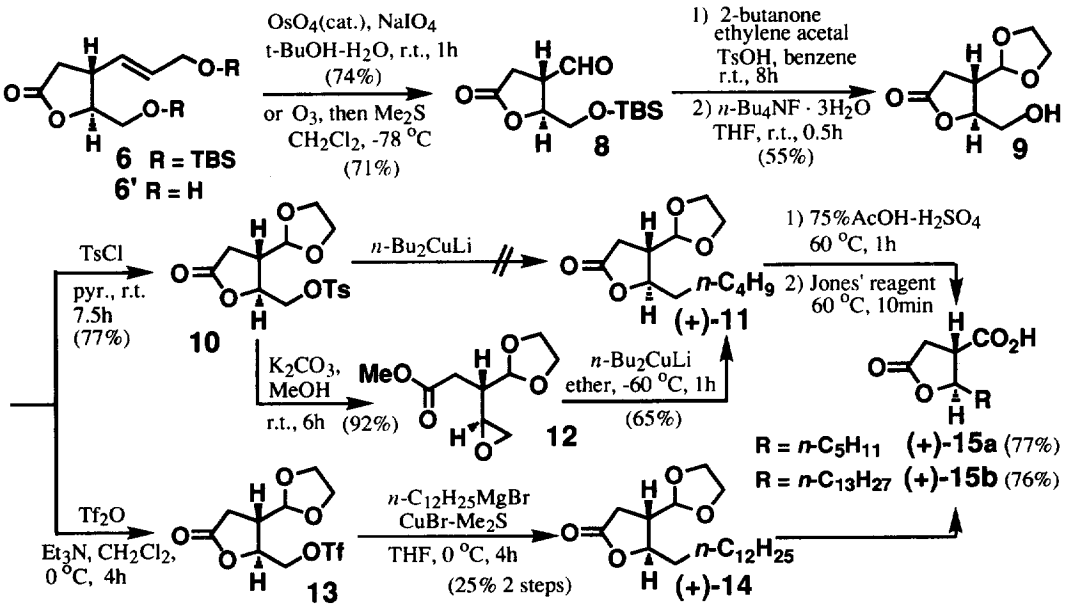


$CH_3CH(OMe)_3$ with catalytic amount of propionic acid under reflux proceeded unsatisfactorily to provide the desired C8-ester in a low yield, application of acetamide-acetal modification of the rearrangement to the C_2-symmetric enediol (**4**) worked satisfactorily. Thus, refluxing the enediol (**4**) with 1.5 equiv of $CH_3C(NMe_2)(OMe)_2$ in benzene for 2.5h in the presence of molecular sieves 4A gave an excellent yield (98%) of the desired C8-amide (**5**) as an oil, structure of which was proposed from the preferred transition state model depicted and characterized by IR ($\nu_{C=O}$ 1636cm^{-1}) and ^{1}H-NMR (2.86; 2.95ppm, 2×3H (s): NMe_2; 5.52; 5.58ppm, 2×1H (d, J=15.1Hz): *trans*-CH=CH-). The amide (**5**) was heated in xylene to provide a lactone (**6**) in 80% yield. X-Ray crystallography[6] on the lactone-diol (**6'**) obtained by desilylation of the lactone (**6**) established the structure not only of the lactone (**6**) but also of the precursor amide (**5**). In turn, treatment of a O-TMS protected amide-alcohol with iodine in aqueous THF at -10 °C afforded an iodo-lactone (**7**) in 74% yield from the amide-alcohol (**5**). The γ-lactone structure was characterized by IR ($\nu_{C=O}$ 1790cm^{-1}) and the stereochemistry of the iodo-lactone (**7**) was verified finally by its conversion into the (-)-lactone acid ((-)-**15a**) (vide infra). Thus, we had both enantiomeric forms of β, γ-disubstituted γ-lactone derivatives (**6**) and (**7**) in hand.

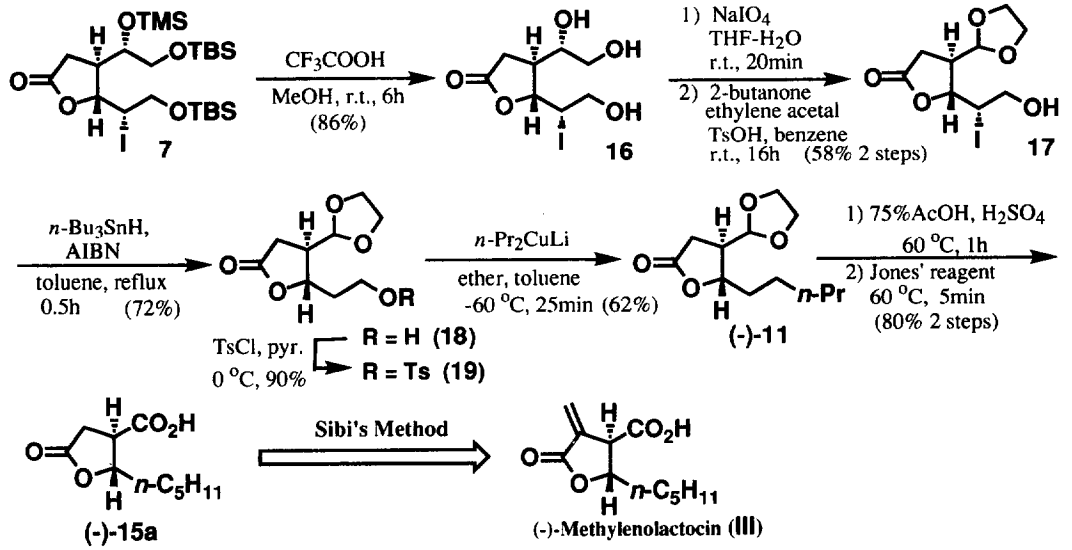


Next, our focus was concentrated on the synthesis of optically active substituted parconic acids (**I**, **II**, **III**). Cleavage of the terminal C2-fragment of the lactone (**6**) either by Lemieux oxidation in aqueous *t*-BuOH or by ozonolysis followed by reductive workup gave an aldehyde (**8**) in good yields. Acetalization followed by desilylation of the aldehyde (**8**) led to 55% yield of a lactone carbinol (**9**), which was converted into the corresponding tosylate (**10**). Although a direct alkylation of **10** with *n*-Bu_2CuLi failed, treatment of an epoxy-ester (**12**),[7] derived quantitatively from the tosylate (**10**), with the cuprate in Et_2O at -60 °C gave an nonanolide ((+)-**11**) in 65% yield. As a trial for another alkylation of the epoxy-ester (**12**) with a mixed cuprate prepared from *n*-$C_{12}H_{25}MgBr$ and CuBr-Me_2S failed, a crude triflate (**13**) of the lactone carbinol was treated with the mixed cuprate in THF at 0 °C gave, albeit in a low yield (25%), a heptadecanolide ((+)-**14**). These γ-alkylated lactones (**11**, **14**) were transformed respectively in 77 and 76% yield through



deacetalization and Jones oxidation to the corresponding carboxylic acids ((+)-**15a**) ($[\alpha]_D$ +54° ($CHCl_3$) and ((+)-**15b**) ($[\alpha]_D$ +39° ($CHCl_3$). These (+)-acids were structurally verified by spectral comparison with the respective authentic data for the corresponding (-)-acids ((-)-**15a**) ($[\alpha]_D$ -54° ($CHCl_3$))[8a] and ((-)-**15b**) ($[\alpha]_D$ -41° ($CHCl_3$)),[8b] and are recognized as the key intermediates for synthesis of (+)-paraconic acids, (+)-protolichesterinic acid (**I**), (+)-roccellaric acid (**II**), and (+)-methylenolactocin (ent-**III**), by Greene's α-methylenation[8] and Sibi's highly stereoselective α-methylation.[9]

Derivation of the iodo-lactone (**7**) to the key synthetic intermediate for (-)-methylenolactocin (**III**) followed. Desilylative deprotection providing a triol (**16**) followed by glycol cleavage with $NaIO_4$, ethylene acetalization of the aldehyde, and deiodination of the iodohydrin (**17**) with n-Bu_3SnH led to an lactone alcohol



(**18**) in 36% overall yield. The corresponding tosylate (**19**) was submitted to alkylation with (n-C_3H_7)$_2$CuLi in Et_2O-toluene at -60 °C to afford 62% yield of another enantiomeric nonanolide ((-)-**11**), which was converted into the (-)-acid ((-)-**15a**) ([α]$_D$ -59° ($CHCl_3$)). The synthesis of the (-)-acid ((-)-**15a**) means a formal total synthesis of natural (-)-methylenolactocin (**III**).[8]

In conclusion, a new chiral C8-building block (**5**) derived from D-mannitol (**1**) was demonstrated to be potential for preparing both enantiomeric forms of β, γ-disubstituted γ-lactones. Further application of the chiral C8-building block (**5**) to the synthesis of optically and biologically active compounds is in progress in our laboratory.

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