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Radical-Mediated Diastereoselective Construction of a Chiral Synthon for Synthesis of Dolabellanes

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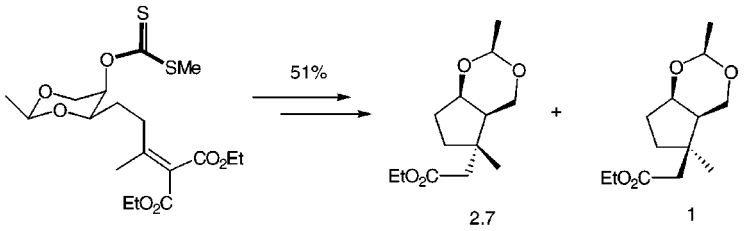
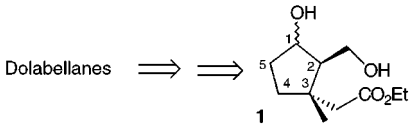
ABSTRACT



A useful *trans*-substituted multifunctional cyclopentane with a chiral quaternary center was selectively synthesized by free radical Michael addition to the (*Z*)-propionate or -malonate derivatives. The stereoselectivity could be reversed by changing the configuration of the double bond.

Dolabellanes[1] are an important class of diterpenoids characterized by the unusual *trans*-bicyclo[9.3.0]tetradecane nucleus. Since the first member reported by Borschberg in 1975, the number of dolabellanes isolated and structurally elucidated has been rising very rapidly.[1] Due to their outstanding bioactivities and unique structures, these types of natural products have attracted much interest[1] from synthetic organic chemists. Most dolabellanes contain a multifunctionalized cyclopentane with a chiral quaternary center, as shown by structure **1**. Therefore, we believe that the latter compound may serve as a versatile building block for enantioselective synthesis of the dolabellanes (Scheme 1) and hence have undertaken a project aiming at developing practical synthetic routes to it. In our previous work,[2] we described an efficient approach to build a multifunctional cyclopentane with a quaternary center. However, the two side chains therein are *cis* to each other instead of the desired

Scheme 1



trans (Scheme 2) for synthesis of dolabellanes. This caused us to develop alternative routes to **1**. Here we wish to report a diastereoselective protocol based on controlling the conformation of the double bond of a radical reaction precursor.

The possible transition state postulated for explaining the high stereoselectivity[2] inspired us to design precursors that may lead to the desired product with two correct chiral centers. The transition state showed that the conformation of the double bond played an important role in the distribution of the *endo* and *exo* forms of the substrate. When the trisubstituted double bond is of *Z* form as in **4**, where the boat conformation is more stable than the chair because the severe repulsion between two large substituents (xanthate

† Fax: 086-021-64166128.

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(2) Zhu, Q.; Qiao, L.-X.; Wu, Y.; Wu, Y.-L. *J. Org. Chem.* **1999**, *64*, 2428−2432.

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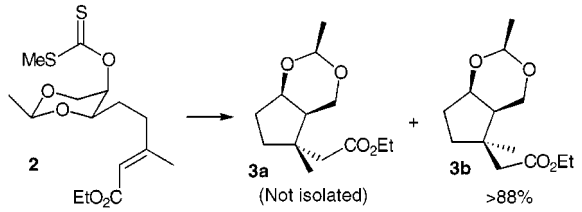
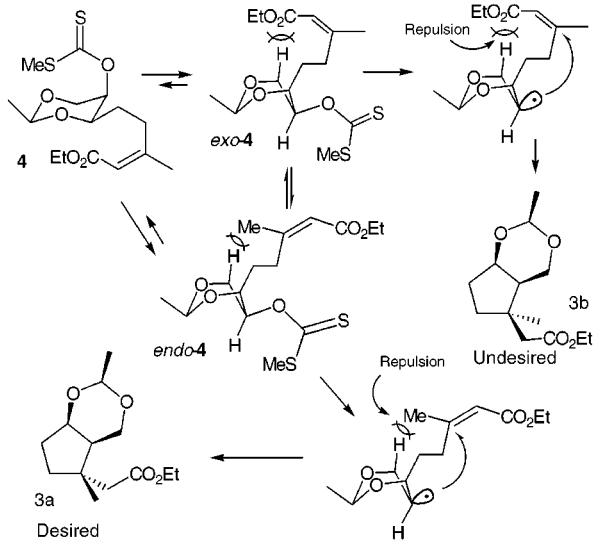
Scheme 2



and the side chain) can be avoided, neither the *endo* nor the *exo* form would predominate over each other due to the repulsion between the hydrogen atom in the 1,3-dioxane and the *exo* ester group or the *endo* vinyl methyl (Scheme 3). Therefore, it is hard to predict which form will be the major one.

Scheme 3



Having noticed the above difficulty, we decided to use the dimethyl precursors **8** and **9** to examine our hypothesis (these compounds with disubstituted *Z* double bonds[3] are much easier to synthesize than the trisubstituted ones; Scheme 4). It is not surprising that the diastereoselectivity drops drastically (from giving practically only *cis* isomer with **2** as radical precursor to a 4.2:1 *cis*/*trans* mixture, presumably because the vinyl methyl is much bulkier than the vinyl hydrogen. When using **9**, the major product was reversed (1:1.2) as we expected, but the diastereoselectivity was still not satisfactory.

It was difficult to determine the absolute configurations of **10a** and **10b** by ^{1}H−^{1}H COSY and ^{1}H−^{1}H NOESY

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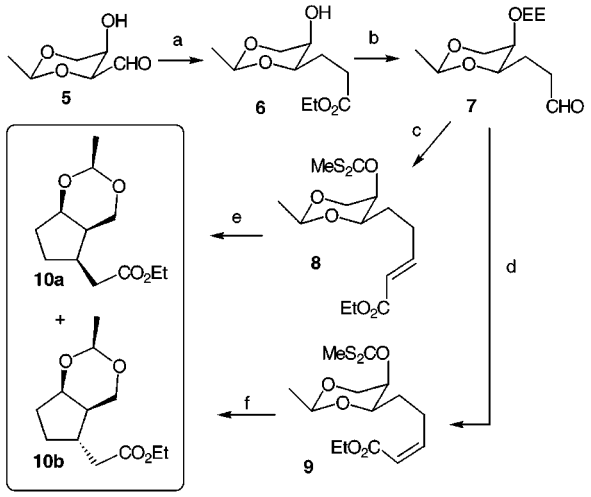
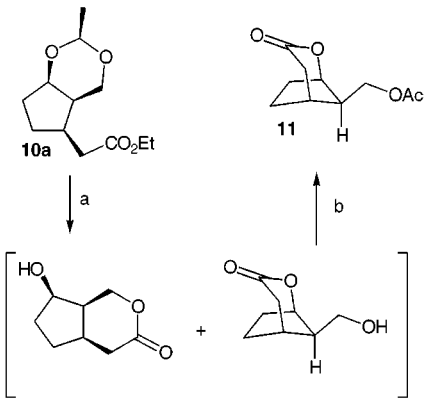
Scheme 4[a]



[a] Reaction conditions: (a) (i) $Ph_3P{=}CHCO_2Et$, THF, (ii) H_2/Pd, MeOH, room temperature, 80%; (b) (i) ethyl vinyl ether, PPTS, CH_2Cl_2, (ii) LAH, THF, (iii) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, 79%; (c) (i) $Ph_3P{=}CHCO_2C_2H_5$, THF, reflux, (ii) 1 N HCl, room temperature, (iii) CS_2, DBU, MeI, DMF, 74%; (d) (i) $(PhO)_2P(O)$-CH_2CO_2Et, NaH, THF, (ii) 1 N HCl, room temperature, (iii) CS_2, DBU, MeI, DMF, 83%, *E*:*Z* = 1:11.5; (e) Bu_3SnH, AIBN, 91%, **10a**:**10b** = 4.2:1; (f) Bu_3SnH, AIBN, 98%, **10a**:**10b** = 1:1.2.

spectroscopy alone. Therefore, we converted (Scheme 5) **10a** into **11**, whose configuration can be easily established without any doubt and thus ensures that the stereochemistry of **10** is indeed as depicted.

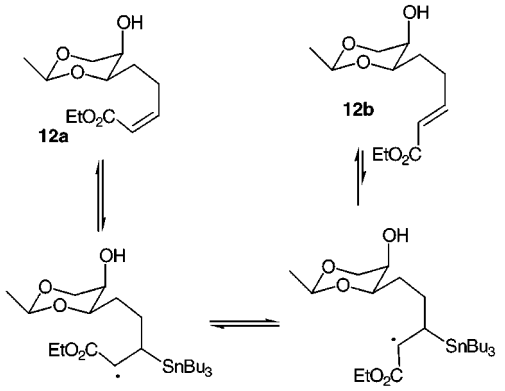
Scheme 5[a]



Introduction of Lewis acids[4] such as $LiClO_4$ and $Yb(OTf)_3$ does not improve the stereoselectivity at all, presumably due to the relatively high temperature employed (refluxing benzene) in the reaction, whereas using the Et_3B/O_2 system[5] failed to drive the reaction to completion even after the mixture was stirred at room temperature for several days. We reasoned that isomerization of the *Z* double bond under the given conditions might be the cause for the poor selectivity. To confirm this hypothesis, we subjected **12a** to

the same reaction conditions. Indeed, **12b** was isolated in 91% yield, contaminated with only a trace amount of **12a** (<1% by NMR) (Scheme 6).

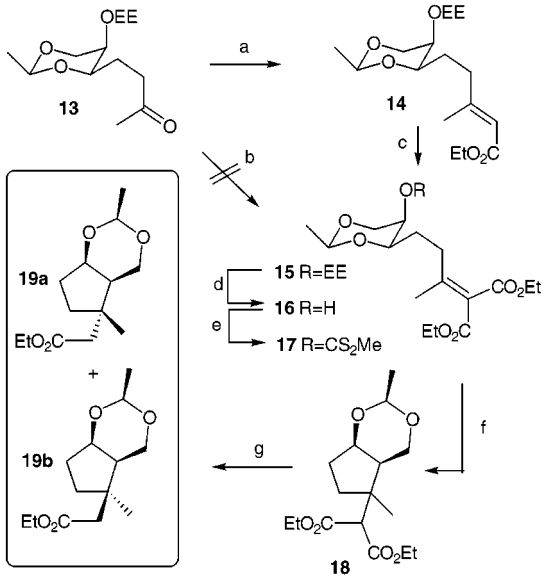
Scheme 6[a]



The route given in Scheme 4 not only offers an efficient approach to **10a** and **10b**, which are useful chiral building blocks for many natural products,[6] but also provides us with important information for designing better precursors to **1**. It appears that the tetrasubstituted olefin **17** as the reaction precursor has a number of advantages (Scheme 7): (1) it is relatively easier to synthesize than the corresponding trisubstituted *Z* olefin, (2) it is the *Z* ester that reacts, and the existence of an *E* ester does not influence the result, and (3) the possible isomerization of the double bond is no longer an interference. Thus, Knoevenagel condensation[7] of methyl ketone **13** with Meldrum's acid and diethyl malonate failed under various conditions. Deconjugation and α-alkylation of the α,*β*-unsaturated ester **14**[8] and the following transformations gave the conjugated tetrasubstituted olefin **17** in a yield of 45%. The radical reaction of **17** gave an inseparable mixture of about 1.5:1 ratio according to the ^{1}H NMR spectrum. Thermal decarboxylation[9] gave a separable mixture of **19a** and **19b** in a 2.7:1 ratio in 51% yield from **17**. Fortunately, the major product is what we desired, by comparison of the spectral data with those for its enantiomer from our previous work. It is apparent that the diester moiety plays an important role in the diastereoselectivity.

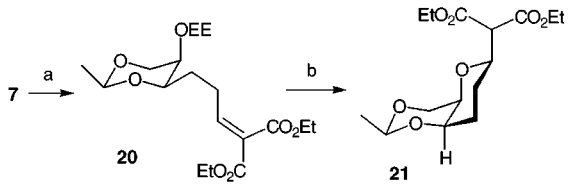
We then tried to introduce the diester moiety in **9**, because this may circumvent the isomerization and improve the selectivity (Scheme 8). The Knoevenagel condensation of **7** with diethyl malonate went smoothly. However, the intramolecular Michael addition product **21** was formed on the silica gel during purification by column chromatography. Fortunately, this did not occur to **16** due to the hindrance of the vinyl methyl.

Scheme 7[a]



[a] Reaction conditions: (a) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 84%; (b) $CH_2(CO_2Et)_2$ or Meldrum's acid; (c) LDA, HMPA, $ClCO_2Et$, −78 to room temperature, 20% of starting material recycled; (d) 1 N HCl; (e) CS_2, DBU, MeI, DMF, 45% from **14**; (f) Bu_3SnH, AIBN, benzene, reflux; (g) DMSO, LiCl, H_2O, 190 °C, 51% from **17**, **19a**:**19b** = 2.7:1.

Scheme 8[a]



[a] Reaction conditions: (a) diethyl malonate 5.0 equiv, *β*-alanine 2.0 equiv, EtOH, 30 °C, 48 h; (b) 1 N HCl, THF, 64%.

Conclusions. The synthesis of a useful *trans*-substituted multifunctional cyclopentane with a quaternary center is described by controlling the conformation of the double bond. The chiral synthon **19a** can be synthesized on a large scale using the inexpensive D-galactose as a chiral pool, which paves the way to the enantioselective synthesis of most dolabellanes. **10a** and **10b** are also useful building blocks for the synthesis of many natural products. The diester moiety is the critical factor for reversing the selectivity at the cyclization step.

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