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Diastereoselective Radical Cyclization of Chiral β-Alkoxyacrylates

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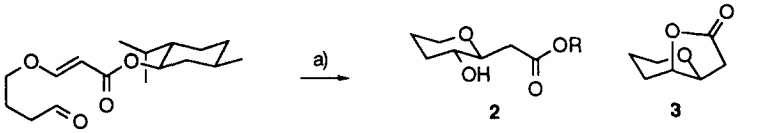
Abstract : *(2R,3S)*-3-Phenylcholestan-2-ol is a moderately effective chiral auxiliary in the radical cyclization of β-alkoxyacrylates. © 1997 Elsevier Science Ltd.

Radical cyclization of β-alkoxyacrylates is now firmly established as an effective method in forming 5- or 6-membered oxacycles.[1] The value of this reaction lies in the fact that only *cis*-2,5-disubstituted tetrahydrofurans and *cis*-2,6-disubstituted tetrahydropyrans are obtained when β-alkoxyacrylates prepared from secondary alcohols are used as substrates. This stereoselectivity may be explained by invoking preference for the *s-trans*(C_β-O) transition state geometry.[1a] More recently, examples of diastereoselective carbocycle formation were reported, in which acrylate substrates containing various chiral auxiliary alcohols were used in radical cyclization reactions.[2] Use of β-alkoxyacrylates obtained from achiral primary alcohols and chiral propiolates may also result in useful degrees of diastereoselection in oxacycle synthesis, and this report concerns our initial results in these areas of studies.

The use of *l*-menthol as the chiral auxiliary generally did not lead to noticeable degree of diastereoselection.[3] But in the case of the aldehyde **1**, 19 % d.e. of the tetrahydropyranyl product **2** was obtained and the lactone product **3** was obtained in 28 % e.e. (Scheme 1).



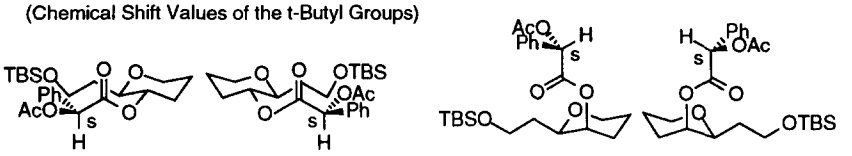
1 **2** 47 % (19 % d.e.) **3** 42 % (28 % e.e.)

a) 1.3 eq. Bu_3SnH, 0.15 eq. AIBN,Benzene (0.03 M), Reflux, 8 h

Scheme 1

In both cases, the diol products , which were obtained after LAH reduction, were derivatized with TBSCl and (*S*)-*O*-acetylmandelyl chloride, and d.e. of each compound was determined by NMR analysis[4] (Scheme 2).

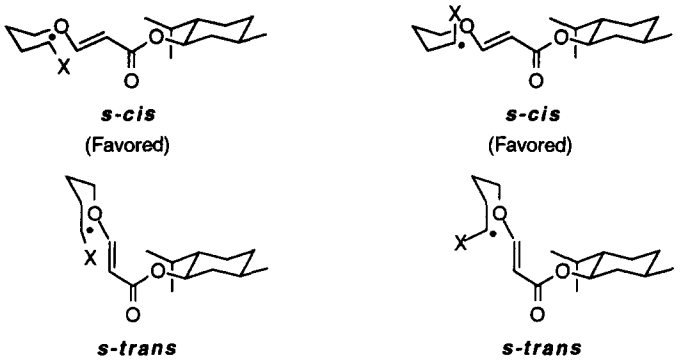
(Chemical Shift Values of the t-Butyl Groups)



δ 0.87 (40.5 %) δ 0.91 (59.5 %) δ 0.88 (36 %) δ 0.84 (64 %)

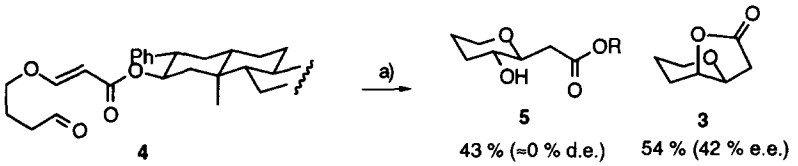
Scheme 2

Assuming that there was a preference for the radical approach away from the isopropyl group, it can be concluded that the *s-cis*(C_{CO}-C_{α}) conformation for the β-alkoxyacrylate moiety was favored in the transition states leading to the products **2** and **3** (Scheme 3).



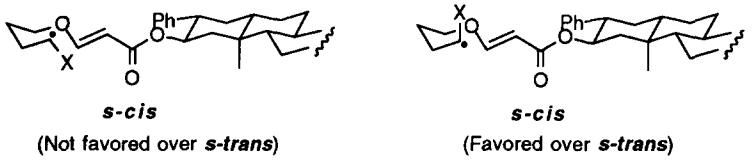
Scheme 3

Encouraged by these results, (*2R,3S*)-3-phenylcholestan-2-ol[5] was chosen as a potentially more effective chiral auxiliary. In the event, the substrate **4** was synthesized following standard procedures[6] and reacted with tributylstannane. In this case, 42 % e.e. of **3** was obtained, but the formation of **5** proceeded



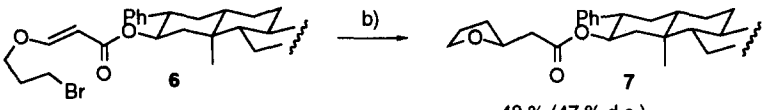
Scheme 4

without any stereocontrol (Scheme 4). It was apparent that the *s-cis* conformation for the trasition state leading to **3** was favored as anticipated, but the expected stereoelectronic preference for the *s-cis* conformation in the transition state leading to **5** did not materialize (Scheme 5).



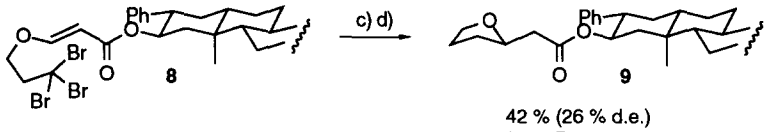
Scheme 5

The usefulness of the chiral auxiliary was tested with different substrates. The 3-bromopropoxy derivative **6** reacted with tributylstannane at -78 °C in the presence of excess boron trifluoride etherate to yield 47 % d.e. of the tetrahydrofuranyl product **7**. In the absence of the Lewis acid, no stereocontrol was observed (Scheme 6). The reactivity of 1,1,1-tribromopropoxy derivative **8** was different. The dibromo substituted radical from **8** was expected to react with a higher degree of stereocontrol, but only simple reduction products were isolated indicating the low reactivity of the dibromo radical in cyclization. When **8** was reacted with tributylstannane under standard high dilution conditions in hot benzene and the products



42 % (47 % d.e.)
(Simple Reduction: 35 %)

* Without $BF_3{\cdot}OEt_2$: 44 % (≈0 % d.e.) (Simple Reduction: 45 %)



42 % (26 % d.e.)
(s.m. Recovery: 21 %)

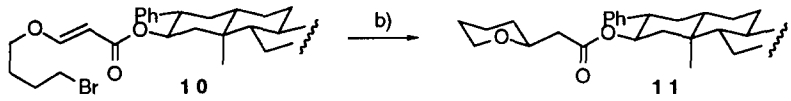
* Only simple reduction products under low temperature conditions.

b) 30 eq. $BF_3{\cdot}OEt_2$, 2.0 eq. Bu_3SnH, 1.5 eq. Et_3B, Toluene (0.02 M), -78 °C, 3 h
c) 1.5 eq. Bu_3SnH, 0.25 eq. AIBN, Benzene (0.03 M), Reflux, 6 h, (Syringe Pump, 5 h)
d) ex. Bu_3SnH, Et_3B, Benzene, r.t.

Scheme 6

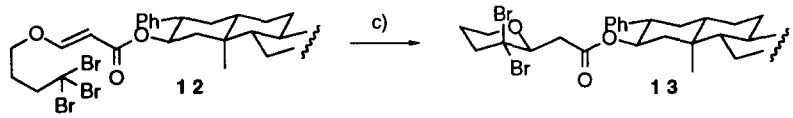
obtained were further reduced with excess tributylstannane, 26 % d.e. of the tetrahydrofuranyl product was obtained favoring the other diastereomer **9**.

For further examination of the stereocontrol in the six-membered ring formation, the reaction of the 4-bromobutoxy derivative **10** was studied. Under normal high temperature/high dilution radical generating conditions, the conversion of **10** into the tetrahydropyranyl product **11** was efficient, but the reaction was non-stereoselective. When **10** was reacted with tributylstannane at -78 °C in the presence of excess Lewis acid, 62 % d.e. of the product **11** was obtained (Scheme 7). Reaction of the 1,1,1-tribromobutoxy derivative **12** under the same low temperature conditions yielded only simple reduction products, confirming the low reactivity of the dibromo radicals in cyclization. The substrate **12** could be converted into the dibromo-tetrahydropyranyl product **13** under high temperature/high dilution conditions, but the cyclization proceeded without any stereocontrol.



33 % (62 % d.e.)
(Simple Reduction: 34 %)

* Under high temperature conditions: 91 % (≈0 % d.e.)

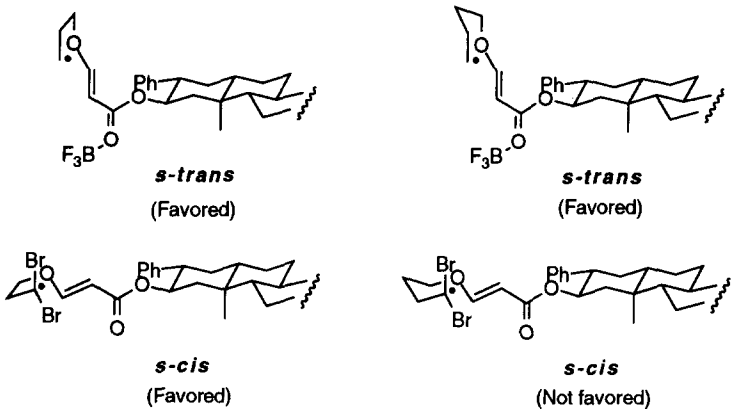


76 % (≈0 % d.e.)

* Only simple reduction products under low temperature conditions.

Scheme 7

From the results obtained, it can concluded that (*2R,3S*)-3-phenylcholestan-2-ol is a moderately effective chiral auxiliary in the radical cyclization of β-alkoxyacrylates. It should be emphasized that under



Scheme 8

the low temperature/Lewis acid conditions, *s-trans* transition state conformation is favored in both 5- and 6-exo cyclizations, whereas *s-cis* conformation is preferred under the high temperature conditions in the absence of added Lewis acids (Scheme 8). The role of Lewis acids in fixing *s-trans* acrylate conformations under radical cyclization conditions was amply discussed by Nishida and coworkers.[2] For the initially strange stereorandom 6-exo cyclizations in the formation of **5** and **13**, one may consider the steric crowding between the pseudoequatorial substituents on the radical carbon and the C-19 methyl group of the cholestanyl auxiliary in the chair-like transition states. Accordingly, use of the bulkier dibromo radicals led to improved stereoselection in the 5-exo cyclization, but not in the 6-exo cyclization. Further developments in these areas of studies will be reported in due course.

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3. The 3-bromopropoxy, 4-bromobutoxy, and 3-butynoxy derivatives gave cyclization products without any stereoselection under the high temperature/high dilution conditions. The reaction of the 3-bromopropoxy derivative yielded less than 5 % d.e. of the tetrahydrofuranyl product at 0 °C in the presence of excess boron trifluoride etherate.
4. For discussions of NMR correlation studies, see: Lee, E.; Lee, Y. R.; Moon, B.; Kwon, O.; Shim, M. S.; Yun, J. S. *J. Org. Chem.* **1994**, *59*, 1444-1456.
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6. (*2R,3S*)-3-Phenylcholestan-2-ol and propiolic acid reacted in the presence of DCC and a catalytic amount of DMAP in ether to give 80 % yield of the propiolate. It was reacted with 1,4-dihydroxybutane in the presence of 0.5 equivalent of tributylphosphane in dichloromethane, and 71 % yield of the 4-hydroxybutoxy derivative was obtained, which was oxidized with PCC to give 92 % yield of **4**.

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