Pergamon

Tetrahedron Letters 42 (2001) 8769–8772

TETRAHEDRON LETTERS

On the stereochemistry of anion-accelerated [1,3]-sigmatropic rearrangement of 2-vinylcyclobutanols

Se-Ho Kim, Sung Yun Cho and Jin Kun Cha*

Department of Chemistry, University of Alabama, Tuscaloosa, AL 35487, USA

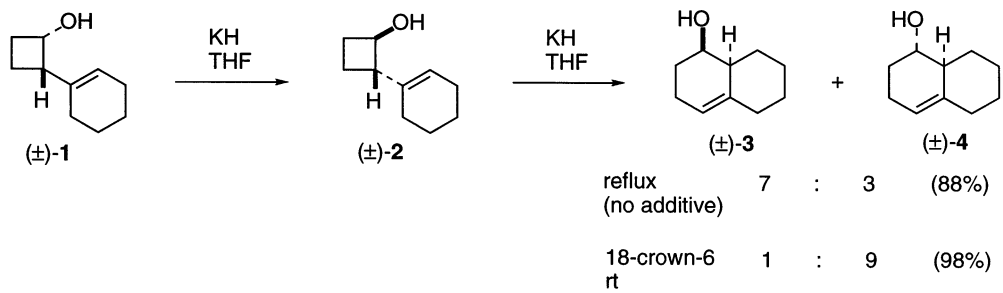
Received 28 August 2001; accepted 10 October 2001

Abstract—Stereochemical studies on the oxyanion-accelerated [1,3]-sigmatropic rearrangement reactions of nonracemic *cis*- and *trans*-2-(1-cyclohexenyl)cyclobutanols are described. Epimerization of *cis*-2-(1-cyclohexenyl)cyclobutanol to the *trans*-isomer at −20°C was found to proceed with predominant retention of configuration, the degree of which was enhanced by an increasing amount of 18-crown-6.

Sigmatropic rearrangements have found frequent use in the stereocontrolled synthesis of organic compounds. When judiciously placed, an anionic substituent provides an enormous rate of acceleration.[1] Since the first example was reported for an oxy-Cope rearrangement,[2] the utility and generality of anion-accelerated sigmatropic rearrangements have been amply demonstrated in natural product synthesis. As shown in Eq. (1),[3e,f] the Danheiser and Cohen groups have elegantly shown that the diastereochemical course of an oxyanion-accelerated [1,3]-sigmatropic rearrangement of a 2-vinylcyclobutanol to the corresponding cyclohexenol product is influenced by the presence or absence of a complexing agent for the metal counterion (e.g. K^+).[3b,e,f,4] Little was known, however, about what level, if any, of enantioselectivity would be observed for the non-concerted rearrangement of a nonracemic 2-vinylcyclobutanol. We describe herein stereochemical studies on the oxyanion-accelerated [1,3]-sigmatropic rearrangement reactions of nonracemic *cis*- and *trans*-2-(1-cyclohexenyl)cyclobutanols (**1** and **2**).[5]

The requisite, nonracemic alcohols **1** and **2** were conveniently prepared via the corresponding cyclobutanone **7** which was produced by the titanium-mediated cyclopropanation of α-hydroxy ester **5a** or **5b** and the subsequent pinacol-type rearrangement of the resulting cyclopropanol **6** (Scheme 1).[6,7] The latter ring expansion reaction, which was achieved by the action of methanesulfonyl chloride (in pyridine) or sequential treatment with sulfuryl chloride–imidazole and Florisil,[6,8] was previously shown to provide **7** with an excellent degree of enantioselectivity. Reduction of this ketone with $NaBH_4$ afforded an easily separable 1:1.8 mixture of (+)-**1** and (−)-**2** in 98% yield. Since both alcohols were desired for stereochemical studies of their rearrangements, no attempt was made to improve the diastereoselectivity of reduction.

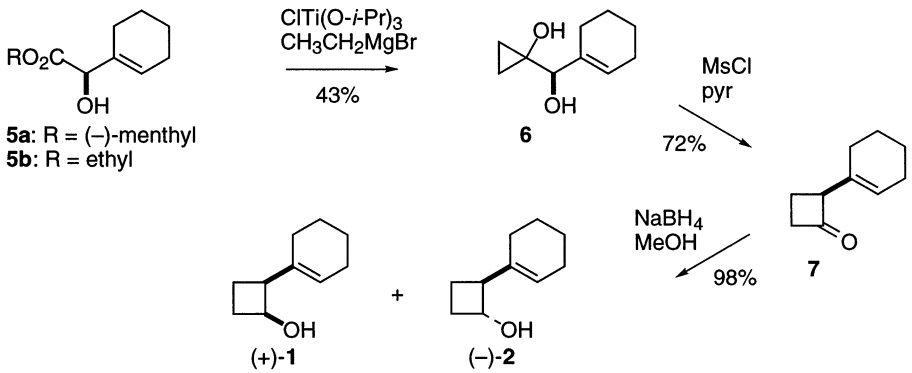
When (−)-*trans*-2-(1-cyclohexenyl)cyclobutanol [(−)-**2**], $[\alpha]_D = -23.9$ (*c* 1.1, CH_2Cl_2), was treated with KH at −25°C for 15–30 min in the presence of 1 equiv. of 18-crown-6 in THF, a facile oxyanion-accelerated rear-



(1)

* Corresponding author. E-mail: jcha@bama.ua.edu

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01929-3

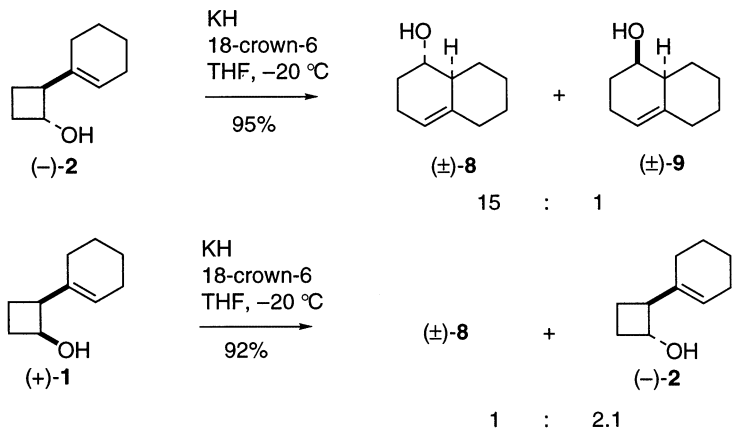


Scheme 1.

rangement took place to give a $\geq$15:1 mixture of *trans*- and *cis*-octalinols **8** and **9** in 95% yield (Scheme 2).[9] The rearrangement of the *cis* isomer (+)-**1**, $[\alpha]_D = +32.3$ (*c* 1.1, CH_2Cl_2), afforded **8** (as the virtually sole isomer), along with varying amounts of the epimerized cyclobutanol which proved to be non-racemic.[10] The yield and enantiomeric purity of the epimerization product (–)-**2** depended upon the reaction time and other variables (vide infra).

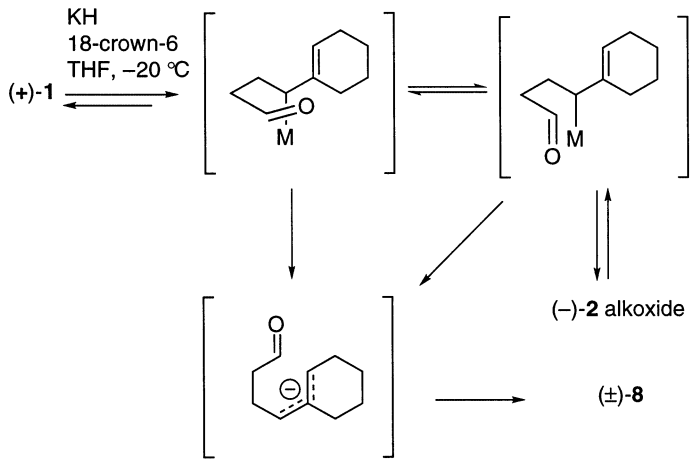
Not surprisingly, the rearrangement products **8** and **9** were shown to be racemic, i.e. identical to (±)-**4** and (±)-**3**, respectively, on the basis of NMR studies of the corresponding acetates (Ac_2O, pyridine) with a chiral shift reagent [Eu(hfc)$_3$]. The thermal [1,3]-sigmatropic rearrangement reactions were also investigated: individual treatment of (+)-**1** and (–)-**2** with KH in refluxing THF for 2 h afforded a $\sim$1.7:1 mixture of (±)-**3** and (±)-**4** in 74% yield in each case.

Gadwood and Cohen had previously observed facile epimerization of *cis*-vinylcyclobutanols to the *trans*-isomers at low temperatures (Eq. (1)).[3d,e] With nonracemic **1**, the key reaction parameters were systematically evaluated to probe the retention of configuration in this *cis*→*trans* isomerization reaction at −25 to −20°C (Table 1). Use of 18-crown-6 was known to accelerate both the epimerization and ring expansion reactions. To ensure reliable reproducibility, an excess (ca. 10 equiv.) of KH was employed. The reaction mixture was quenched in 20–40 min when most of the starting alcohol had disappeared.[11] The products were then analyzed by the ^{1}H NMR and/or GC/MS methods, where material balance was excellent in all cases. Epimerization took place with retention of configuration. Remarkably, the degree of enantioselectivity was controlled primarily by the amounts of 18-crown-6: whereas the *trans*/*cis* diastereoselectivity for formation of **8** was independent of (catalytic or stoichiometric) quantities of 18-crown-6,[3f] the enantioselectivity of epimerization [i.e. (+)-**1**→(–)-**2**] was enhanced by an increasing amount of this complexing agent. For example, when 1 equiv. (entry 2) and 2.6 equiv. (entry 5) of 18-crown-6 were employed, **2** was obtained in 54 and 90% ee, respectively. This striking influence of quantities of 18-crown-6 on the level of enantioselectivity seemed at first counter-intuitive: epimerization, which primarily involves the different orientation of the aldehyde with respect to the allylic anion, takes place faster than racemization of an allylic anion/aldehyde intermediate (Table 1 where M depicts a pair of electrons; the complexing agent and the solvent are omitted for clarity). The difference in the relative rates of these two competing processes apparently becomes larger with an increasing amount of 18-crown-6, presumably because of greater dissociation of the potassium ion and hence higher reactivity of the resulting allylic anion intermediate. Subsequent rotation of the bond between the cyclohexenyl ring and the side chain, which is required for the ring closure to the *trans*-octalinol product, leads to



Scheme 2.

Table 1.



Entry	KH (equiv.)	18-Crown-6 (equiv.)	Product ratio[b] (**2**:**8**:**1**)	ee of **2**[c] (%)
1	11	0.5	2.4:1:0.4	33
2	11	1.0	2.3:1:0.1	54
3	9.2	1.3	2.5:1:0.2	72
4	10	1.5	2.5:1:0.1	84
5	11	2.6	2.17:1:0.02	90
6[a]	10	2.7	2.74:1:0.21	83[a]

[a] Reaction conditions: THF (0.02 M), except for entry 6 (0.01 M), −25 to −20°C, 20 to 40 min.
[b] Determined by the ^{1}H NMR spectra (for entries 1–4) or GC (for entries 5 and 6).
[c] Determined by comparison of optical rotation and/or NMR studies with Eu(hfc)$_3$.

racemization.[12] Finally, the alkoxide of the epimerized alcohol **2** is not believed to be an obligatory intermediate for **1**→**8**, at least at −25 to −20°C, but is directly involved in epimerization and also ring closure.

In summary, both thermal and potassium alkoxide-accelerated [1,3]-sigmatropic rearrangements of non-racemic 2-(1-cyclohexenyl)cyclobutanols were found to take place with complete loss of chirality, that confirmed the accepted mechanism involving the non-concerted, fragmentation–rearrangement pathway.[3,4] On the other hand, the new finding that facile epimerization of (+)-**1** to (−)-**2** at −20°C took place with predominant retention of enantiomeric purity should be of mechanistic and preparative interest.[13]

Acknowledgements

We thank the National Science Foundation (CHE98-13975) for financial support.

References

1. For excellent reviews, see: (a) Bronson, J. J.; Danheiser, R. L. In *Comprehensive Organic Syntheses*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, pp. 999–1035; (b) Wilson, S. R. *Org. React.* **1993**, *43*, 93.
2. Evans, D. A.; Golob, A. M. *J. Am. Chem. Soc.* **1975**, *97*, 4765.
3. For recent examples, see: (a) Wilson, S. R.; Mao, D. T. *J. Chem. Soc., Chem. Commun.* **1978**, 479; (b) Danheiser, R. L.; Martinez-Davila, C.; Sard, H. *Tetrahedron* **1981**, *37*, 3943; (c) Zoeckler, M. T.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 7661; (d) Gadwood, R. C.; Lett. R. M. *J. Org. Chem.* **1982**, *47*, 2268; (e) Cohen, T.; Bhupathy, M.; Matz, J. R. *J. Am. Chem. Soc.* **1983**, *105*, 520; (f) Bhupathy, M.; Cohen, T. *J. Am. Chem. Soc.* **1983**, *105*, 6978; Cf. (g) Cohen, T.; Yu, L.-C.; Daniewski, W. M. *J. Org. Chem.* **1985**, *50*, 4596.
4. For a detailed mechanistic study of the 1,3-sigmatropic shift of vinylcyclobutanol alkoxides, see: Harris, N. J.; Gajewski, J. J. *J. Am. Chem. Soc.* **1994**, *116*, 6121.
5. A chiral ketal was employed to probe the mechanism for the lithium alkoxide-induced [1,3]-rearrangement of a vinyl benzocyclobutene: Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 1800.
6. Cho, S. Y.; Cha, J. K. *Org. Lett.* **2000**, *2*, 1337.
7. For an enantioselective preparation of **5b** by enzymatic kinetic resolution, see: Vankar, P. S.; Bhattacharya, I.; Vankar, Y. D. *Tetrahedron: Asymmetry* **1996**, *7*, 1683. We have found that the use of *Candida rugosa* was superior to that of PLAP, affording the alcohol **5b**, $[\alpha]_D = -84.7$ (*c* 1.15, $CHCl_3$), in an excellent level of enantioselectivity and in the opposite sense.
8. Nemoto, H.; Fukumoto, K. *Synlett* **1997**, 863.
9. The *cis*/*trans* nomenclature for octalinols refers to the relative stereochemistry of the two methine hydrogens.
10. (a) After 4 h at −20°C, the anion-assisted rearrangement of (+)-**1** gave a 20:1 mixture of **8** and **2** in 96% yield. (b) The rearrangement of (+)-**1** was slower than that of (−)-**2** under the reaction conditions employed, suggesting that ring opening of **1** was the slowest step.

11. There was no appreciable change in enantiomeric purity of recovered **1**.
12. For each of the species drawn in Table 1, there are two possible geometrical isomers. The second one (not shown) cannot possibly undergo ring closure, but may as well be responsible for some of epimerization noted.
13. Although speculative at this point, the anionic oxy-Cope rearrangement of non-racemic *trans*-dialkenylcyclobutanols,[3c] which would be readily available from addition of a suitable alkenyllithium to **7**, might provide enantiomerically pure substituted 4-cyclooctenones by way of the initial isomerization of the *trans*-→*cis*-dialkenylcyclobutanols free from racemization.