Ring expansions of (*R*)-(–)-carvone to cycloheptenoid chirons

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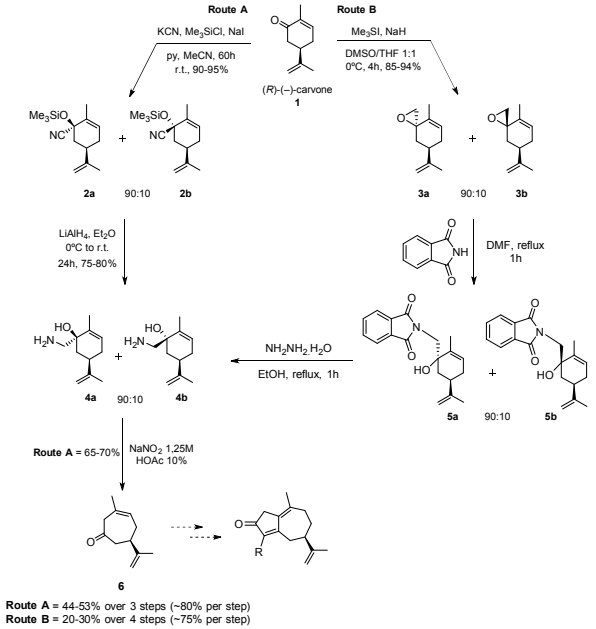
(R)-(–)-carvone; ring expansion; cycloheptenone, X-ray structure assignment

INTRODUCTION

In the course of our studies on the synthesis of perhydroazulene terpenes,[1] we have developed a synthetic route (Scheme 1, Route A) to the cycloheptenone chiron **6** from (*R*)-(–)-carvone (**1**). Herein we present our corrected structural assignment of **4a**,[2] as confirmed by X-ray analysis, and describe an attractive alternative route towards **6** (Scheme 1, Route B).

RESULTS AND DISCUSSION

The formation of the TMS-protected cyanohydrins **2a** and **2b** and the Corey-Chaykovsky epoxidation to **3a** and **3b**, led to 90:10 ratios determined by GC and NMR analysis of *trans*:*cis* nucleophilic addition relative to the isopropenyl group of (*R*)-(–)-carvone (**1**).



Scheme 1. Synthetic routes from (*R*)-(–)-carvone (**1**) to the cycloheptenone **6**.

The corrected assignment of the stereochemistry[2] of **2a** was made by X-ray diffraction (Figure 1) and nOe irradiations of the major amino-alcohol **4a**, obtained by reduction of the cyanohydrin mixture **2a**/**2b**.

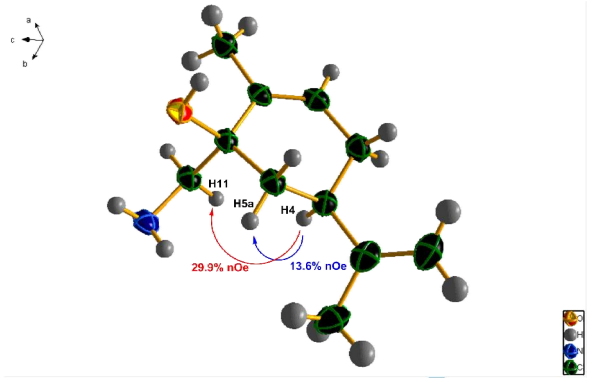


Figure 1. Structure of the major amino-alcohol **4a** obtained by X-ray diffraction, and indication of observed nOe. (Ellipsoids shown at 40% probability level).

Epoxide opening of **3a**/**3b** (Scheme1, route B) was accomplished by phthalimide in DMF at reflux. Hydrazinolysis of the phthalimido-alcohols **5a** and **5b** produced the same amino-alcohols **4a**/**4b** obtained in Route A. The last step is the totally regioselective Tiffeneau-Demjanov rearrangement, which leads to the key intermediate cycloheptenone **6**.

CONCLUSION

Addition of the two nucleophiles to (*R*)-(–)-carvone (**1**) was determined to be 90:10, in favour of the *trans* relationship to the isopropenyl group. A new synthetic route to **6** is presented with advantages of scaling up, minimum usage of chromatography, and avoiding the use of cyanide.

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REFERENCES

[1] Brocksom, T. J., Brocksom, U., Sousa, D. P, Frederico, D. *Tetrahedron Asym.*, **2005**, *16*, 362. Faria, M. L; Magalhães, R. A.; Silva, F. C.; Matias, L. G. O.; Ceschi, M. A.; Brocksom, U; Brocksom, T. J. *Tetrahedron Asym.*, **2000**,*11*, 4093

2. Alves, L de C.; et al. 14th BMOS, 2011.