



The enantioselective synthesis of key intermediates for the synthesis of (+)-brevifloralactone from *R*-(-)-carvone

V. Olkhovik,^a N. Masalov,^b B. J. M. Jansen^c and Aede de Groot^{c,*}

^aLaboratory of Organic Chemistry, Institute of New Materials Chemistry, Belarus Academy of Sciences, str. Kuprevicha 16, 220141 Minsk, Belarus

^bDepartment of Organic and Polymer Chemistry, Belarussian State University, F. Skoriny av. 4, 220050 Minsk, Belarus

^cLaboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands

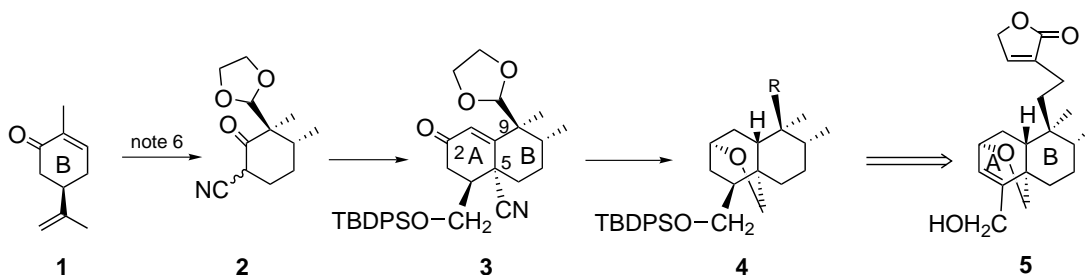
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Abstract—Starting from *R*-(-)-carvone, a sequence of reactions has been developed for the enantioselective synthesis of key intermediates, which contain ether and hemiacetal bridges that are present in antifeedant clerodanes such as brevifloralactone and jodrellin. © 2001 Elsevier Science Ltd. All rights reserved.

Clerodanes occur widely in Nature,^{1,2} and many show interesting physiological properties, of which antifeedant activity is the most documented one.² Only a few clerodanes with an ether bridged ring A such as brevifloralactone (**5**) and jodrellin are found in Nature, and this bridge seems to be important for strong antifeedant activity. The synthesis of clerodanes³ is still a challenging problem, and until now only one method has been published for the construction of a bridged intermediate that may be suitable for the total synthesis of jodrellin A.⁴ In this paper a new approach for the construction of a key intermediate in the synthesis of brevifloralactone (**5**), containing this characteristic ether bridge over ring A, is described. For this synthesis new methodology concerning the introduction of substituted sidechains in carvone (**1**)⁵ and regarding the Robinson annulation of heavily substituted cyclohexanones⁶ has been developed, which gives an

easy access to intermediates of type **3**. The addition of MVK to α -cyano ketone **2** under Knoevenagel conditions, led to good yields of annulated products with the desired *trans* position of the nitrile group at C5 and the major substituent at C9. Simultaneously, suitable functional groups at C5 and C2 are obtained that can serve for the construction of the ether bridge over ring A (Scheme 1).

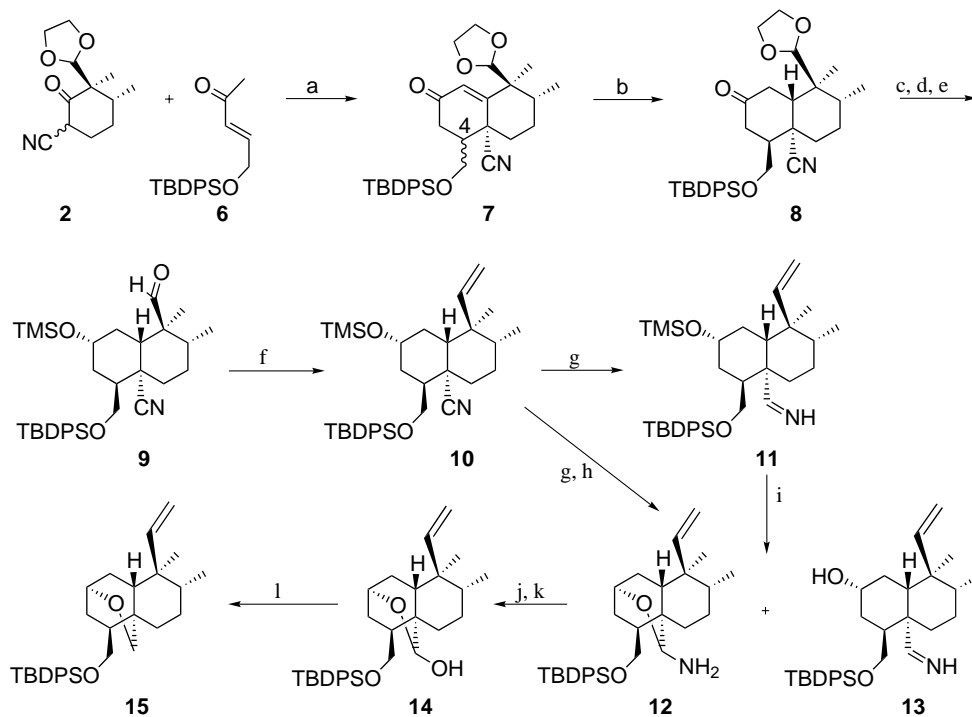
It was found that this annulation also proceeds smoothly when substituted enones such as **6**⁷ are reacted with cyano ketone **2**⁶ (Scheme 2). The annulated product **7** was obtained in 86% yield as a 2:1 mixture of products epimeric at C4, with the compound with the protected hydroxy methylene substituent in the axial position as main product (vide infra) (Scheme 2). For the synthesis of brevifloralactone, the configuration at C4 is not of great importance because in this



Scheme 1.

Keywords: carvone; clerodane; synthesis; α -cyano ketones.

* Corresponding author. Tel.: +31-317-482370; fax: +31-317-484914; e-mail: aede.degroot@bio.oc.wag-ur.nl



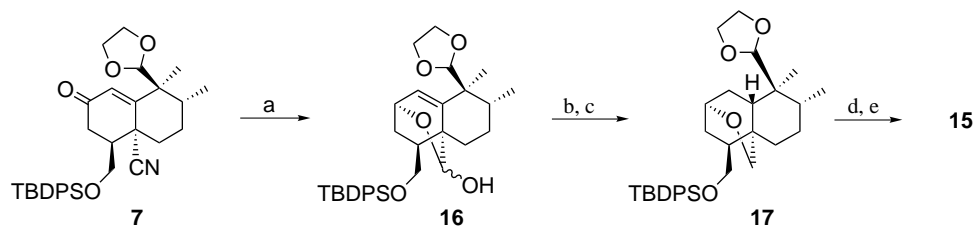
Scheme 2. Conditions: (a) pyrrolidine, toluene, Δ , 65%; (b) H_2 , Pd/C, MeOH, 93%; (c) $NaBH_4$, *i*-PrOH, 0°C; (d) PPTS, acetone, H_2O , Δ , 84% (two steps); (e) TMSCl, Et_3N , THF, rt, 98%; (f) Ph_3PCH_3Br , BuLi, THF, -20 to 0°C, 92%; (g) DIBAH, toluene, 0–20°C, 95%; (h) K_2CO_3 , MeOH, 0°C, 40 min, quant.; (i) H^+ , H_2O ; (j) $NaNO_2$, AcOH, dioxane, H_2O , 92%; (k) HCl, dioxane, rt; (l) Et_3SiH , CF_3CO_2H , CH_2Cl_2 , 88% (two steps).

molecule a double bond is present at the Δ^3 position. The mixture could be separated by column chromatography and the next experiments have been performed with the indicated major epimer. Catalytic reduction of the $\Delta^{10,11}$ double bond gives **8** with the correct configuration at C10. It seemed appropriate to introduce the Δ^3 double bond in this stage of the synthesis, prior to reduction of the carbonyl group at C2 and the nitrile at C5. However, reduction of **7** with DIBAH or $LiAlH_4$ also caused elimination of the nitrile group and DIBAH gave ring opening of the dioxolane group. Therefore, the dioxolane group was converted first into a methylene group, which should be inert during the reduction of the nitrile and at the same time could serve as precursor for the construction of the brevifloralactone side chain.⁷

Thus, the carbonyl group at C2 in **8** was reduced stereoselectively to an α -hydroxyl group, the dioxolane was hydrolyzed to an aldehyde and the C2 hydroxyl

group was protected as its trimethylsilyl ether **9**. The aldehyde was converted, via a Wittig reaction, into the corresponding methylene derivative **10** in high yield and now the nitrile group could be reduced with DIBAH to give the imine **11** in 85% yield.

It turned out that this imine is a stable compound and its hydrolysis under different acidic conditions gave only an equilibrium mixture consisting of the unprotected imine **13** and its intramolecular cyclization product **12**. The same mixture was formed from **11** when just the trimethylsilyl group was hydrolyzed. A nearly quantitative yield of the mixture of **12** and **13** was obtained when the crude product after reduction with DIBAH was treated with K_2CO_3 in methanol at 5°C. Further hydrolysis of this mixture could only be accomplished by treatment with sodium nitrite, to give the hemiacetal **14**. The reduction of crude **14** was performed with trifluoroacetic acid and triethylsilane to give the desired cyclic ether **15**⁸ in 88% yield.



Scheme 3. Conditions: (a) DIBAH (10 equiv.), toluene, $-78^\circ C$, then HOAc, H_2O ; (b) Et_3SiH , CF_3CO_2H , CH_2Cl_2 , 70% (two steps); (c) H_2 , Pd/C, MeOH, 50 h; (d) PPTS, acetone, H_2O , reflux, 71% (two steps); (e) Ph_3PCH_3Br , BuLi, THF, -20 to 0°C, 60%.

Later, it was discovered that a shorter route to **15** (Scheme 3) could be realized via low temperature reduction of **7** with DIBAH, which gave directly a mixture of hemiacetals **16** in good yield after acidic work-up. This mixture was reduced further to the cyclic ether and hydrogenated to compound **17**. Hydrolysis of the dioxolane and a Wittig reaction again gave compound **15** in 30% overall yield from **7**. NMR experiments on ether **15** showed that no NOE effect was present between the methylene protons on the ether bridge and the protons of the protected hydroxymethylene group at C4. This led to the conclusion that the substituent at C4 occupies the axial position.

Thus, a sequence of reactions has been developed, which is suitable for the construction of molecules with ether bridges such as **14** and **15**, as they are present in active antifeedant clerodanes like jodrellin and brevifloralactone, respectively.

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8. All compounds showed correct spectral data and exact mass spectral data. The spectral data of **15** are: $[\alpha]_D^{20} = -34.6$ ($c = 1.07$, CDCl_3); $^1\text{H NMR}$ (CDCl_3 , 200 MHz) δ 0.73 (d, $J = 6$ Hz, 3H), 1.01 (s, 3H), 1.04 (s, 9H), 1.13–1.86 (m, 11H), 3.54–3.63 (m, 2H), 3.73–3.85 (m, 3H), 4.91 (dd, $J_1 = 18$ Hz, $J_2 = 1.4$ Hz, 1H), 5.03 (dd, $J_1 = 10$ Hz, $J_2 = 1.4$ Hz, 1H), 5.43 (dd, $J_1 = 18$ Hz, $J_2 = 10$ Hz, 1H), 7.34–7.47 (m, 6H), 7.63–7.69 (m, 4H); $^{13}\text{C NMR}$ (CDCl_3 , 50 MHz) δ 10.6 (q), 16.7 (q), 19.3 (s), 26.4 (t), 26.8 (q), 28.4 (t), 31.2 (t), 32.5 (t), 33.3 (s), 40.5 (d), 44.3 (s), 45.6 (d), 46.9 (d), 64.2 (t), 65.3 (t), 66.0 (d), 112.8 (t), 127.6 (d), 129.6 (d), 133.8 (s), 133.9 (s), 135.6 (d), 149.1 (d); IR ν_{max} (liquid film) 3070, 2955, 2930, 2856, 1427, 1112, 1071, 1050, 1000, 909, 824, 739, 702; HRMS calcd for $\text{C}_{28}\text{H}_{35}\text{O}_2\text{Si}$ ($\text{M}-57$)⁺ 431.2406, found 431.2403 ($\sigma = 0.098$ mmu).