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The first total synthesis of (±)-junicedranol based on a novel anionic [1,3] rearrangement

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Abstract

The racemate of junicedranol, a sesquiterpene-alcohol with a novel carbon skeleton, was prepared through a unique anionic [1,3] rearrangement of an 8-methylenebicyclo[3.2.1]oct-6-en-2-ol giving a cyclopentadiene derivative and the facial- and regioselective Diels–Alder reaction of the cyclopentadiene with a ketene equivalent leading to the junicedranol framework. © 2000 Elsevier Science Ltd. All rights reserved.

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Junicedranol **1**, a sesquiterpene with a new carbon skeleton, has recently been isolated from *Junipers oxycedrus* ssp. *macrocarpa*, by Barrero and co-workers.[1] The unique tricyclic structure with the four contiguous quaternary carbon centers makes junicedranol **1** a challenging synthetic target. For example, a biomimetic cyclization-approach to (±)-**1** has already been examined and (±)-6-epijunicedranol **2** has been obtained (Fig. 1).[2]

1 **2** **3** **4**

Fig. 1.

Very recently, we have reported an anionic [1,3] rearrangement leading to a [5–6] fused-ring compound, such as compound **4**, from the *trans* oxy-Cope system including a methylidene bridge such as compound **3**.[3] Diels–Alder reaction of the cyclopentadiene **4** with a ketene-equivalent proceeded

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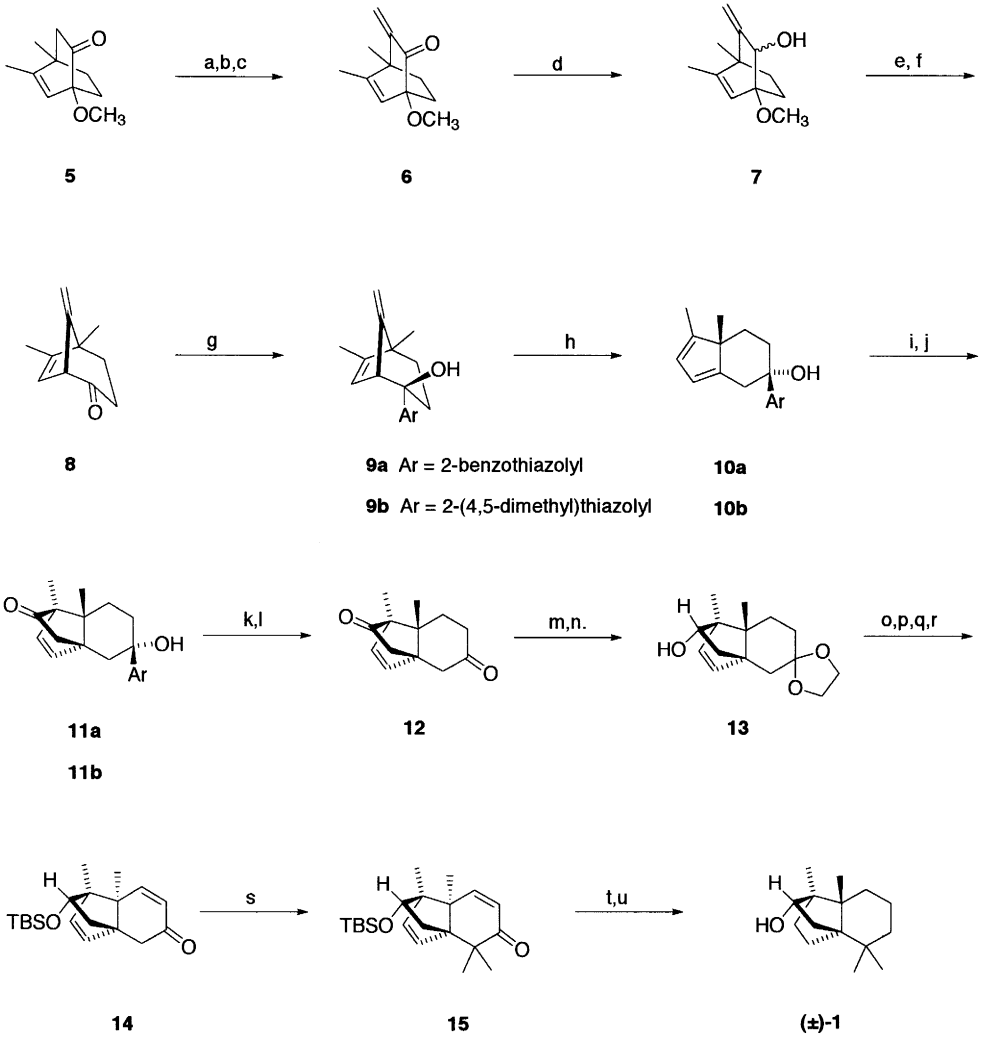
on the convex giving mainly *ortho* orientation products[4–7] whose carbon framework is very similar to that of junicedranol. Consequently, we attempted the total synthesis of (±)-**1** using the anionic [1,3] rearrangement followed by the Diels–Alder reaction strategy as listed in Scheme 1 in order to elucidate the synthetic utility of the rearrangement.†



Scheme 1. Total synthesis of (±)-junicedranol based on the anionic [1,3] rearrangement followed by Diels–Alder reaction: (a) LDA, CH_3I–HMPA, THF; (b) KHMDS, $CH_2{=}CHCH_2COCl$; (c) $Pd(OAc)_2$, CH_3CN; (d) $NaBH_4$–$CeCl_3$, CH_3OH; (e) $(C_2H_5)_3N$, MsCl, ether; (f) NaI, DMF; (g) *n*-BuLi, benzothiazole or 4,5-dimethylthiazole, THF; (h) KH, THF, reflux; (i) $CH_2{=}CHCN$, toluene, reflux; (j) LDA, O_2, THF, then Na_2SO_3, H_2O; (k) CH_3I, DMF; (l) 10% K_2CO_3, H_2O, PhH, reflux; (m) $(CH_2OH)_2$, TsOH, PhH, reflux; (n) Na, *i*-PrOH, toluene; (o) AcOH, CH_3OH, H_2O; (p) TBSCl, imidazole, DMF; (q) LDA, TMSCl, THF, then NBS, THF; (r) LiBr, Li_2CO_3, DMF; (s) NaH, *t*-BuOH (30 mol%), CH_3I, THF; (t) H_2, 5% Pd–C, C_2H_5OAc; (u) H_2NNH_2–2HCl, $CH_2(CH_2OH)_2$, then KOH, Δ

The lithium enolate of 4,5-dimethylbicyclo[2.2.2]oct-5-en-2-one **5** was treated with iodomethane in THF at −78°C in the presence of HMPA. The resulting α-methyl ketone, derived in 82% yield, was

† All new compounds reported here exhibit satisfactory spectral characteristics including HRMS.

converted into the potassium enolate and then treated with allyl chloroformate. Treatment of the allyl enol carbonate with palladium(II) acetate[8] in boiling acetonitrile gave the α,β-unsaturated ketone **6** in 81% overall yield.

Reduction of the conjugated ketone **6** in a 1,2-fashion using $NaBH_4$–$CeCl_3$ in methanol[9] gave a mixture of stereoisomeric alcohols **7** in 95% yield. Attempts to obtain the bicyclo[3.2.1]oct-6-en-2-one **8** through pinacol-type rearrangement of **7** by treatment with *p*-toluenesulfonic acids were practically unsuccessful. The alcohols **7** were transformed into a mixture of the methanesulfonates, and then the mixture was treated with sodium iodide in DMF[10] to give the desired ketone **8** in 75% overall yield.

The substituent Ar of bicyclic alcohol **9** should act as an activating group for the anionic [1,3] rearrangement leading to a [5–6] fused-ring compound.[3] Then the substituent must be cleaved easily to generate a carbonyl group. In addition to these steps, if the Ar should act as a protective group for the carbonyl during preparation of another carbonyl group, such as that of **11**, the synthetic route could be shortened.

Our first choice for the substituent Ar was a 2-benzothiazolyl group, which had already been used as carbonyl equivalents.[11] A reaction of 2-benzothiazolyl lithium and the ketone **8** at −78°C in THF gave alcohol **9a** in 72% yield as the major product. Treatment of the alcohol **9a** with potassium hydride in boiling THF, mainly gave the [1,3] rearrangement product **10a** in 71% yield.

A reaction of **10a** with acrylonitrile at 120°C gave a mixture of four kinds of Diels–Alder adducts. The mixture was treated successively with lithium diisopropylamide in THF, with oxygen, and then with 1 M aqueous sodium sulfite solution. Chromatographic separation gave the desired ketone **11a** in 71% overall yield. In order to regenerate the carbonyl group by removing the heterocyclic substituent,[11] *N*-methylation of **11a** was attempted under various conditions. So far, the yields of the *N*-methyl derivative were less than 50%. Treatment of the *N*-methyl derivative with a boiling mixture of 10% aqueous potassium carbonate solution and benzene gave the desired diketone **12** in 47% overall yield from **11a**.

Then a 2-(4,5-dimethyl)thiazolyl group was employed for activation of the [1,3] rearrangement instead of the 2-benzothiazolyl group. The *exo*-alcohol **9b** was derived as the major product in 72% yield from **8**.

The anionic [1,3] rearrangement of **9b** gave the [5–6] fused-ring compound **10b** in 85% yield. Tricyclic-bridged ketone **11b** was derived in 86% overall yield from **10b** by a very similar method to that employed for preparation of **10a**. The two-step transformation of **11b** into the diketone **12** proceeded smoothly, giving the latter in an 88% overall yield.

The cyclohexanone of **12** was protected as a 1,3-dioxolane in 96% yield. Reduction of the resulting mono-ketone with sodium and 2-propanol in toluene[12] at 25°C gave, selectively, the thermodynamically more stable alcohol **13** in 82% yield. The dioxolane was cleaved by treatment with a mixture of acetic acid, methanol, and water (4:1:1) giving a keto-alcohol, and then the hydroxyl group was protected as *t*-butyldimethylsilyl (TBS) ether (84% overall yield). Several attempts for regioselective alkylation to form the *gem*-dimethyl group were unsuccessful at this stage.

Regioselective bromination of the ketone through the kinetically-controlled trimethylsilyl enol ether, followed by dehydrobromination using lithium bromide and lithium carbonate in DMF, gave the α,β-unsaturated ketone **14** in 80% overall yield from the saturated ketone. Treatment of **14** with sodium hydride, iodomethane, and 2-methyl-2-pronanol (30 mol%) in THF gave the desired *gem*-dimethylation product **15** in 67% yield. The tetrahydro-derivative of **15** was obtained in 83% yield by catalytic hydrogenation using 5% Pd on C in ethyl acetate. Wolff–Kishner reduction[13] of the tetrahydro-derivative gave an alcohol in 23% yield whose spectroscopic characteristics are identical with those of junicedranol **1**.

In conclusion, the practical value of the anionic [1,3] rearrangement of an 8-methylenebicyclo-[3.2.1]oct-6-en-2-ol to the [5–6] fused-ring system, including a cyclopentadiene part, was elucidated by the first total synthesis of (±)-junicedranol.

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