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A novel method for the synthesis of diquinanes based on anionic [1,3] rearrangement of bicyclo[3.2.1]oct-6-en-2-ols

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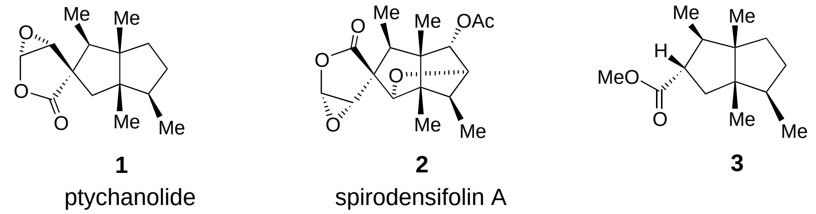
Abstract—The synthesis of unique diquinanes, possessing four continuous methyl groups on the convex of the diquinane skeleton, has been achieved by employing a combination of pinacol-type rearrangement and efficient anionic [1,3] rearrangement strategies.

Sesquiterpene lactones, ptychanolide **1**[1] and spirodensifolin A **2**,[1c] were isolated from the Liverwort *Ptychanthus striatus* Ness and *Frullanoides densifoloia* Radii, respectively. These compounds are unique diquinanes, because they possess an epoxidized spiro-γ-lactone moiety and four contiguously-oriented methyl groups on the convex of the diquinane skeleton. Therefore, these compounds became synthetic targets for organic chemists. Although many approaches for the synthesis of diquinanes have been reported,[2] no total synthesis of ptychanolide **1** and spirodensifolin A **2** has yet been achieved (Fig. 1).

In the course of our studies on the synthesis of natural products, we have already investigated practical rearrangement methods from a bicyclic system to an [m–n] fused-ring system.[3] Recently, we have reported a novel method for the synthesis of [5–5] fused-ring compounds, the so-called diquinanes, via an anionic [1,3] sigmatropic rearrangement[4] of bicyclo[3.2.1]oct-6-en-2-ols.[3c] We report herein a novel strategy for the synthesis of the diquinane **3**, which can be considered as a potential synthetic intermediate for ptychanolide **1** and its related compounds, by employing a combination of the pinacol-type rearrangement[5] and the anionic [1,3] rearrangement, as depicted in Scheme 1.

A starting material, 1-methoxy-4,5-dimethylbicyclo[2.2.2]oct-5-en-2-one **4**, already introduced two methyl groups to the desirable positions. Compound **4** was prepared by Diels–Alder reaction[6a] of 1-methoxy-3,4-dimethyl-1,3-cyclohexadiene and acrylonitrile, followed by oxidation of the resulting nitriles.[6b] The lithium enolate derived from **4** was treated with iodomethane in THF at −78°C in the presence of HMPA to afford a ketone **5** as the sole product in 97% yield.[†] The introduction of the third methyl group in **5** proceeded stereoselectively. Treatment of **5** with *p*-



1
ptychanolide

2
spirodensifolin A

3

Figure 1.

Keywords: diquinanes; ptychanolide; anionic [1,3] rearrangement; bicyclic compounds.

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

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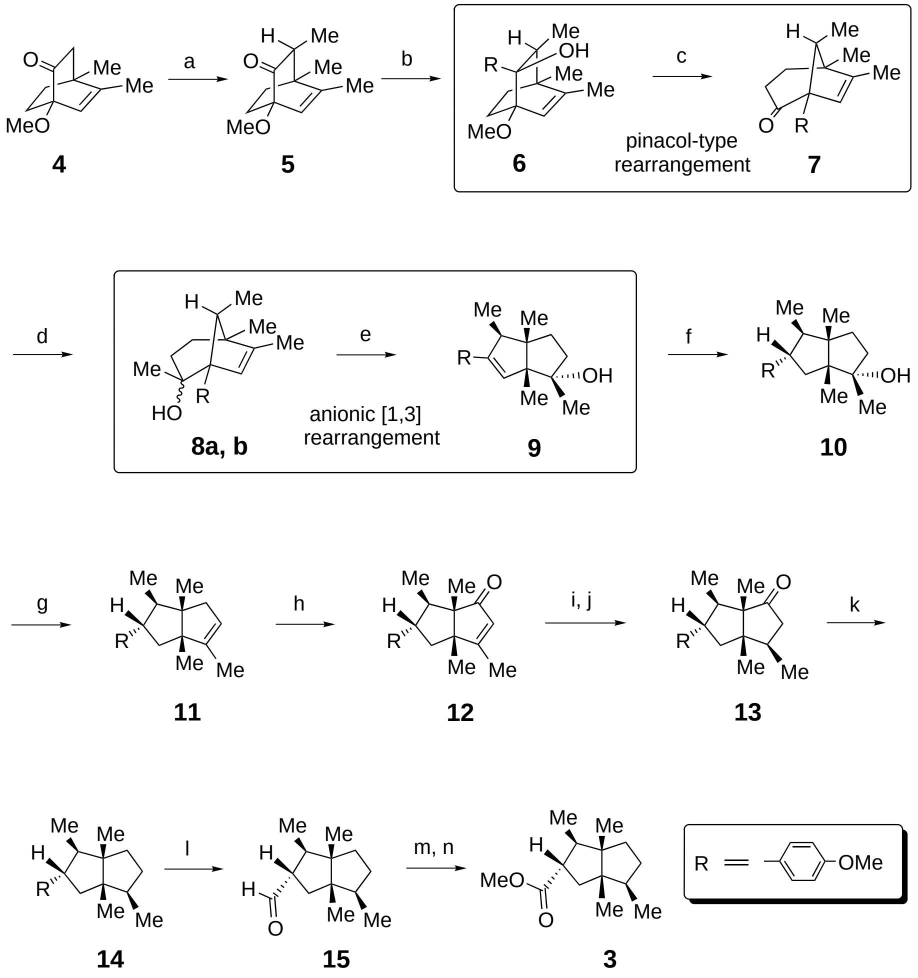


Scheme 1. *Reagents and conditions*: (a) LDA, MeI–HMPA, THF, 97%; (b) *p*-MeOC$_6$H$_4$MgBr, THF, 94%; (c) *p*-TsOH, PhH, 50%; (d) MeLi–CeCl$_3$, THF, 80%; (e) KN(TMS)$_2$, toluene, 87%; (f) H$_2$, 10% Pd–C, EtOH, 99%; (g) KHSO$_4$, toluene, 83%; (h) CrO$_3$, 3,5-dimethylpyrazole, CH$_2$Cl$_2$, 61%; (i) liq. NH$_3$, Li, NH$_4$Cl, THF; (j) TPAP, NMO, 4 Å MS, MeCN, two steps 71%; (k) hydrazine, K$_2$CO$_3$, triethylene glycol, 62%; (l) O$_3$, MeOH, then Me$_2$S, 47%; (m) Ag$_2$O, MeOH–H$_2$O, 66%; (n) CH$_2$N$_2$, Et$_2$O, 54%.

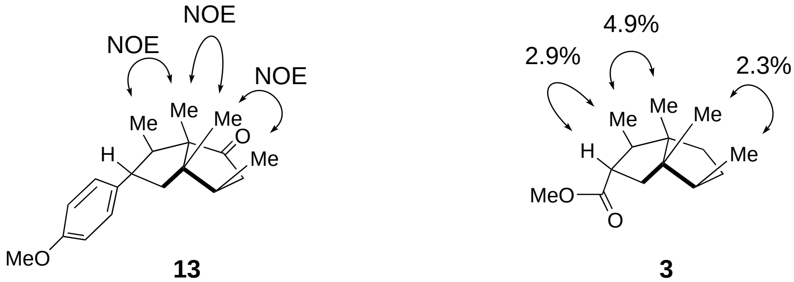
methoxyphenylmagnesium bromide at room temperature gave **6** as a single isomer in 94% yield.

The effects of substituent R on the following pinacol-type and [1,3] rearrangements were then examined. As the result, we concluded that the *p*-methoxyphenyl group is the most suitable substituent for these rearrangements. The pinacol-type rearrangement of **6** with *p*-toluenesulfonic acid yielded a bicyclo[3.2.1]oct-6-en-2-one **7**, which on methylation with MeLi–CeCl$_3$ in THF converted into a mixture of diastereoisomers **8a** and **8b** in 80% yield. On the other hand, the pinacol-type rearrangement of phenyl derivative **16** gave two ketones (**17**, **18**) in a ratio of 42:58, of which the major product was an undesired ketone.[7]

Treatment of the mixture (**8a**, **8b**) with potassium bis(trimethylsilyl)amide [KN(TMS)$_2$] in toluene at 80°C gave the desired diquinane **9** as a single isomer in 87% yield. This result indicated that the anionic [1,3] rearrangement proceeded stereoselectively.[3c] The selective hydrogenation of **9** with 10% Pd–C in EtOH was achieved in quantitative yield to give diquinane **10**. Dehydration of **10** also proceeded to afford **11** in good yield by using KHSO$_4$ in refluxing toluene.

Several attempts to derive from **11** the diquinane **14**, possessing four contiguous methyl groups on its convex, revealed that the Birch reduction pathway is the best. The diquinane **11** was then converted into an α,β-conjugated ketone **12** in 61% yield by chromium trioxide. Birch reduction of **12**, followed by re-oxidation with TPAP–NMO in MeCN gave the desired ketone **13** in 71% overall yield, because the resulting saturated ketone **13** in the former reaction was partially reduced to give a saturated alcohol.

The relative stereochemistry of **13** was determined by the NOESY spectrum, in which two bridgehead methyl groups showed strong NOEs with the adjacent methyl groups. Therefore, the four contiguous methyl groups have a *syn*-relationship to one another, as shown in Fig. 2.



13 **3**

Figure 2. NOE correlations in the diquinanes **13** and **3**.

Wolff–Kishner reduction of the ketone **13** gave **14** in 62% yield. In order to apply the methodology to the synthesis of natural products, the *p*-methoxyphenyl group of **14** must be converted into another suitable functional group. Ozonization of the diquinane **14**, followed by reduction with Me_2S gave an aldehyde **15** in yield 47%. A furyl group is generally known as a formyl equivalent.[8] Attempts to improve the yield of ozonolysis by using the furyl group were however unsuccessful; the anionic [1,3] rearrangement of the furyl derivatives corresponded to **8** gave the corresponding diquinane in poor yield accompanied by the decomposition of the furyl group. The aldehyde **15** was then oxidized into the corresponding carboxylic acid in 66% yield by using Ag_2O. Finally, the carboxyl group was esterified into methyl ester **3** in 54% yield. The stereochemistry of the ester **3** was also confirmed by its NOE difference spectra, as depicted in Fig. 2.

In conclusion, we have developed a novel methodology for the construction of unique diquinanes, possessing four contiguous methyl groups on their convex, by employing a combination of pinacol-type rearrangement and anionic [1,3] rearrangement. This strategy would be applicable to the total synthesis of natural diquinanes, such as ptychanolide **1** and its related compounds.

Acknowledgements

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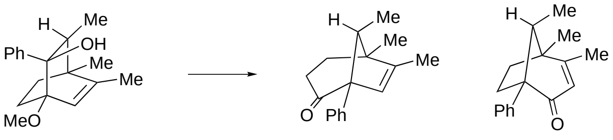

16 **17** **18**

42 : 58

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