Tetrahedron Letters, Vol.32, No.10, pp 1279-1282, 1991
Printed in Great Britain

0040-4039/91 $3.00 + .00
Pergamon Press plc

A NOVEL SYNTHESIS OF JUNCUSOL

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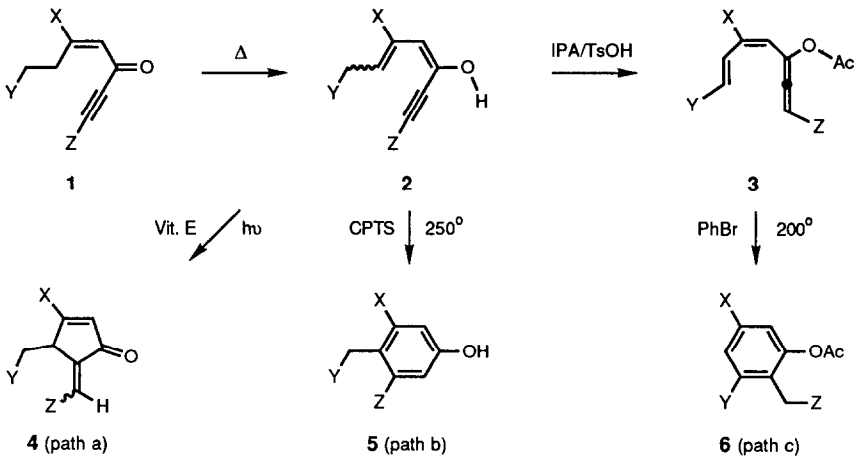
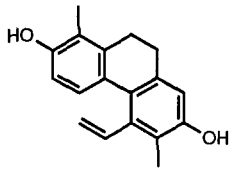
Summary: *Juncusol (7) has been prepared by a novel electrocyclization process beginning with the known ß-tetralone derivative 9.*

In a recent series of papers we have reported that enynones of general structure **1** undergo a number of novel cyclization reactions, the nature of which can be readily controlled by a proper choice of experimental conditions.[1] A common intermediate in these cyclizations is the enolyzed species **2**, which upon photoassisted electron transfer is transformed to methylenecyclopentenones of type **4** with excellent selectivity (> 95%) and in high chemical yield (80 - 98%, *path a*).[1b] This mode of cyclization has now been employed in the synthesis of the antibiotic

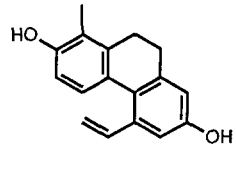


methyleneomycin B and also in the synthesis of various spirocyclic compounds related to acorone.[1a, 2] In the absence of suitable electron donors the mode of reactivity of **2** is quite different. Under conditions of simple acid catalysis **2** is converted to highly substituted phenols of type **5** (80 - 90% yield, > 90% selectivity, *path b*), while in the presence of acylating agents **2** is converted to the isomeric phenol acetates **6**, again in high yield and with excellent selectivity (*path c*). We believe that this last transformation involves the intermediate formation of the conjugated allene derivative **3**, which upon electrocyclic ring closure and tautomerization affords **6**.[3] Simple ester cleavage then provided the parent phenols. In this note we describe the application of this methodology to the

synthesis of juncusol (**7**) (type *c* cyclization),[4] and some model studies directed toward the synthesis of effusol (**8**) (type *b* cyclization).[5] Juncusol (**7**) has been found to possess interesting antimicrobial and cytotoxic properties,[4b] which include action against human epidermoid carcinoma of the nasopharynx.

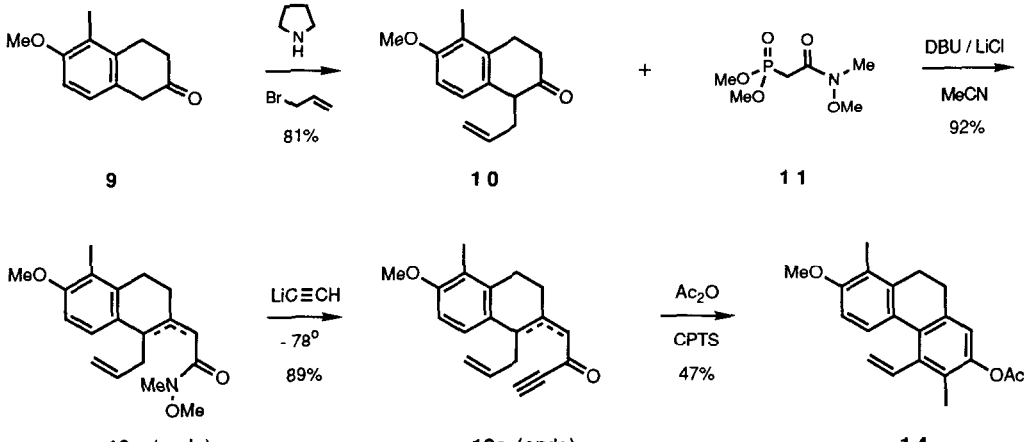


Juncusol (**7**)



Effusol (**8**)

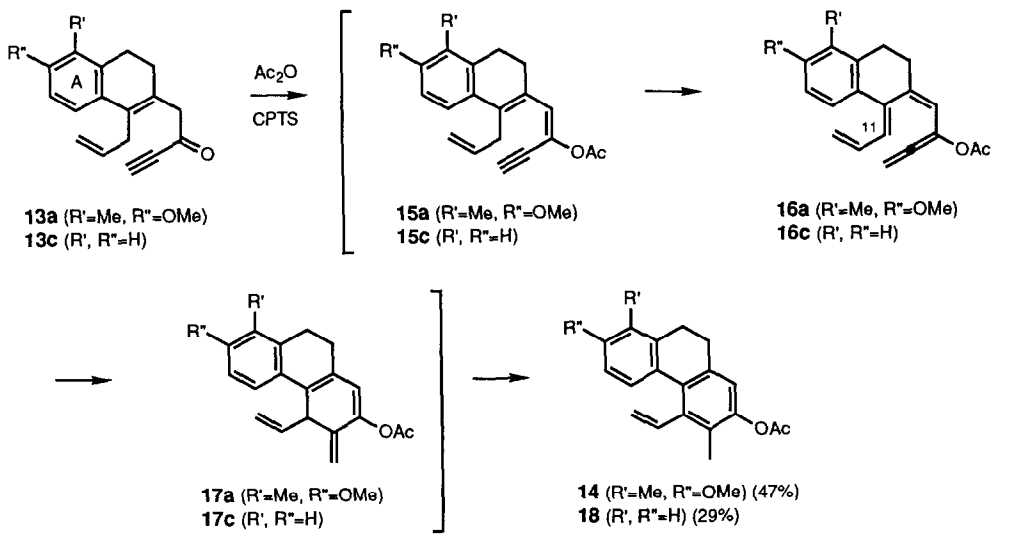
The starting material for our synthesis of **7** was the known ß-tetralone derivative **9** (Scheme 1), which was readily prepared in multigram quantities following the procedure of Schultz *et al.*[6a] Attempted mono-alkylation of the sodium enolate of **9** with allyl bromide invariably led to substantial amounts of bis-alkylated material.[6b] However, the pyrrolidine enamine of **9** underwent smooth mono-alkylation to afford the desired intermediate **10** in excellent yield.[7] Next, **10** was directly converted to the unsaturated amide **12** by reaction with the Wittig reagent **11**[8] employing the general conditions of Masamune and Rousch (92% yield).[9] The material thus obtained consisted of an ~ 4.5 : 1 mixture of *endo* and *exo* isomers, which were initially separated and carried through the synthesis individually. However, it was subsequently found that separation at this stage was unnecessary since both sets of isomers reacted in nearly identical fashion. Pure *endo* amide **12a** afforded an 89% yield of *endo* enynone **13a** upon condensation with lithium acetylide, and interestingly, pure *exo* amide **12b** also gave predominantly (~ 6 : 1) *endo* enynone **13a** under identical conditions. Furthermore, both **13a** and **13b** underwent cyclization to give the protected diphenol **14** under substantially the same conditions. In our original studies we found that the reagent system isopropenyl acetate (IPA) and TsOH provided the best yields for transformations of this type in simple



Scheme 1

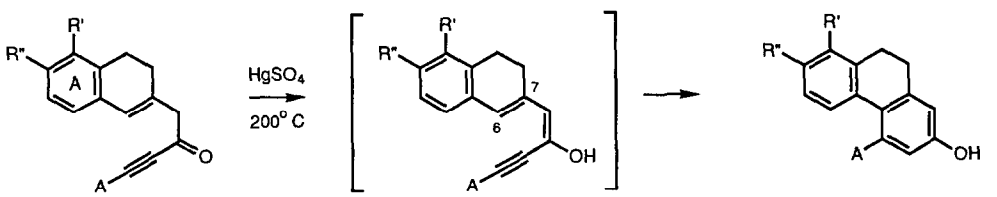
model systems.[1c] In the present case the most satisfactory results were obtained with neat acetic anhydride as the acylating reagent and collidine *p*-toluenesulfonate (CPTS) as the acid catalyst. Thus, **13a** afforded a 47% yield of **14** upon heating at 160° C for 3 h with Ac_2O/CPTS, and **14** was then converted to juncusol (**7**), mp 172.7-173.7° C, in 73% yield with LiSMe in HMPA (23% overall yield from **9**).[4f] The material thus obtained was identical in all respects with an authentic sample.[10]

Cyclizations of type *c* are accelerated by the presence of electron donating substituents on ring A. Thus, **13c** reacted only sluggishly to afford the phenol acetate **18** (29%) under identical conditions as those employed for the conversion of **13a** to **14** (Scheme 2).[11] These results are consistent with the intermediacy of the allenyl acetates **16a,c**, in which the methoxyl group in **16a** increases the nucleophilicity at C_{11} by its resonance effect.



Scheme 2

In contrast, cyclizations of type *b* are inhibited by electron donating substituents on ring A. Thus, **19a** gave a 44% yield of the phenol **21a** upon heating at 200° C with CPTS in dichlorobenzene (18 h), and a 64% yield of **21a** with $HgSO_4$ in dichlorobenzene. In contrast, **19b** afforded only 14% of **21b** under both sets of reaction



conditions. In this case, we believe, the methoxyl group tends to decrease nucleophilicity at C_6 relative to C_7 by its resonance effect, thereby working in opposition to the electron donating effect of the enolic hydroxyl functionality. In no case were we able to observe measurable quantities of effusol precursor **21c** upon acid catalyzed cyclization of **19c**. These last experiments were also hindered by the extreme acid and base lability of precursor **19c**.[12] In principle, electron withdrawing groups at C_2 (R") should accelerate cyclizations of type *b*, and we are currently exploring this possibility for the synthesis of effusol (**8**).[13,14]

References and Notes

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3. See, for example, (a) Okamura, W. H.; Peter, R.; Reischl, W. *J. Amer. Chem. Soc.* **1985**, *107*, 1034. (b) Okamura, W. H.; Elnagar, H. Y. *J. Org. Chem.* **1988**, *53*, 3060.

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8. Wittig reagent **11** was prepared by reaction of bromoacetyl bromide with N,O-dimethylhydroxylamine to afford the corresponding bromoamide, followed by Arbusov reaction with trimethyl phosphite: Pale yellow oil, $Bp_{0.06}$ 105 - 108° C. **CAUTION**: On two occasions explosions occurred upon attempted distillation at a slightly higher pressure than that reported above. Compound **11** is thermally unstable above 110° C. The diethoxy Wittig reagent corresponding to **11** is now commercially available from the Aldrich Chemical Company; see also Nuzillard, J.-M.; Boumendjel, A.; Massiot, G. *Tetrahedron Lett.* **1989**, *29*, 3779.

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10. We are grateful to Professor Dale Boger, of Purdue University, for providing an authentic sample of **7**.

11. We are grateful to Mr. David Skibbie for initially preparing compound **13c**.

12. All attempts at cyclizing **19a-19c** under the basic conditions recently reported by Corey *et al.* also led to rapid decomposition of starting materials: *cf.*, Corey, E. J.; Carpino, P. *J. Am. Chem. Soc.* **1989**, *111*, 5472.

13. Satisfactory analytical and spectral data were obtained for all new compounds reported.

14. Financial support of this work by the National Science Foundation, Grant #CHE-9001485, is gratefully acknowledged.

(Received in USA 13 December 1990)