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A new enantiospecific synthetic procedure to the taxoid-intermediate 10-methylenecamphor, and 10-methylenefenchone

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Abstract—A new straightforward enantiospecific synthetic procedure to both 10-methylenecamphor and 10-methylenefenchone, from (+)-camphor and (−)-fenchone, respectively, is described. 10-Methylenecamphor is the key intermediate in Paquette's approach to taxol and taxusin, whereas 10-methylenefenchone could be a convenient intermediate to a new family of potentially interesting taxoids. The key steps of the described procedure are: (a) stereocontrolled tandem electrophilic carbon–carbon double-bond addition-Wagner–Meerwein rearrangement of a camphor- or fenchone-derived 2-methylenenorbornan-1-ol under Eschenmoser's salt treatment, and (b) Cope elimination for generation of the vinyl group at the bridgehead norbornane position.

Taxane diterpenes, such as the well-known taxol **1**, taxusin **2** or taxinini **3** (Fig. 1), are an important family of isolated yew-tree natural products with special biological activities.[1] Thus, taxol, which discloses a unique remarkable capacity for stabilizing microtubule assembly and deterring cell division,[2] is one of the most important drugs against a number of human cancers (e.g. in refractory ovarian, breast and lung cancers);[3] whereas taxusin, taxinini and other taxanes are known to inhibit the drug-transport activity of P-glycoprotein,[4] showing valuable multi-drug resistance-reversing activity.[5]

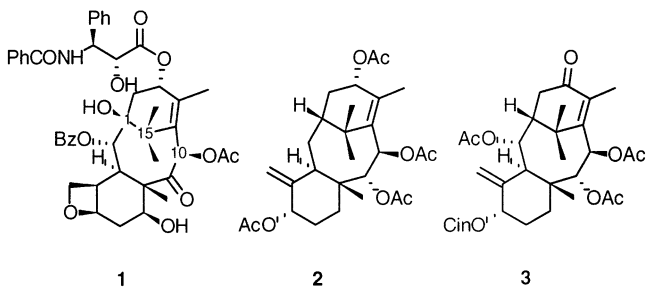

Figure 1. Some interesting taxane diterpenes.

The complex basic structure of taxanes, a tricarbocyclic moiety containing an anti-Bredt carbon–carbon double bond as well as a large number of oxygenated asymmetric centers (see Fig. 1), makes their synthesis very complicated. Thus, taxanes remain as some of the most challenging targets in natural-product synthesis.[6]

Among the most interesting approaches to taxanes,[6] the elegant approach of Paquette must be outlined.[6i–k] This approach has been used for the total synthesis of natural (−)-taxol and (+)-taxusin and it is based on the use of (1*S*)-10-methylenecamphor **4a** as a key intermediate (Scheme 1).[6i–k] Unfortunately, although intermediate **4a** is obtained from commercial 10-camphorsulfonyl chloride **5** with good yield (71%), according to the procedure described by Fischer and Opitz in 1973,[7] it requires the use of dangerous diazomethane to form an unstable episulfone intermediate (Scheme 1).[7]

On the other hand, we have recently reported on the enantiospecific preparation of (1*S*)-10-dimethylaminomethylcamphor **6a** by Eschenmoser's salt treatment of (1*R*)-3,3-dimethyl-2-methylenenorbornan-1-ol **7a** (Scheme 2).[8] The process takes place with an interesting tandem electrophilic carbon–carbon double-bond addition - Wagner–Meerwein rearrangement.[8] Intermediate **7a** is easily obtained from commercial natural (1*R*)-camphor **8a** according to a procedure previously described by us.[9]

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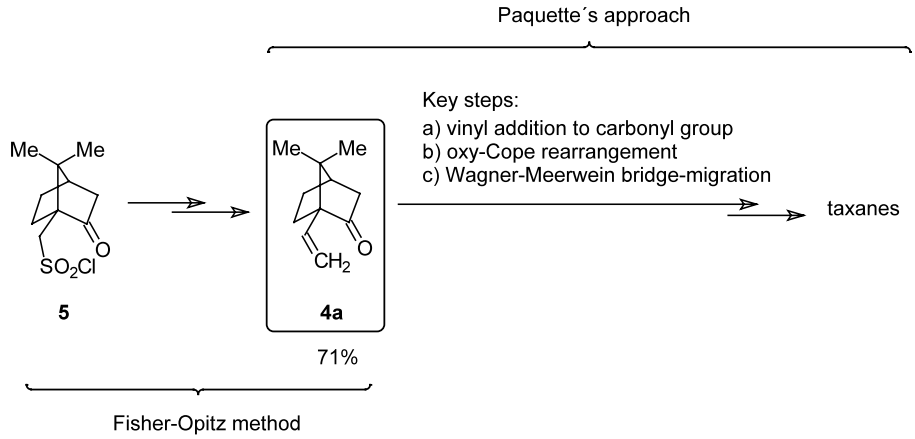


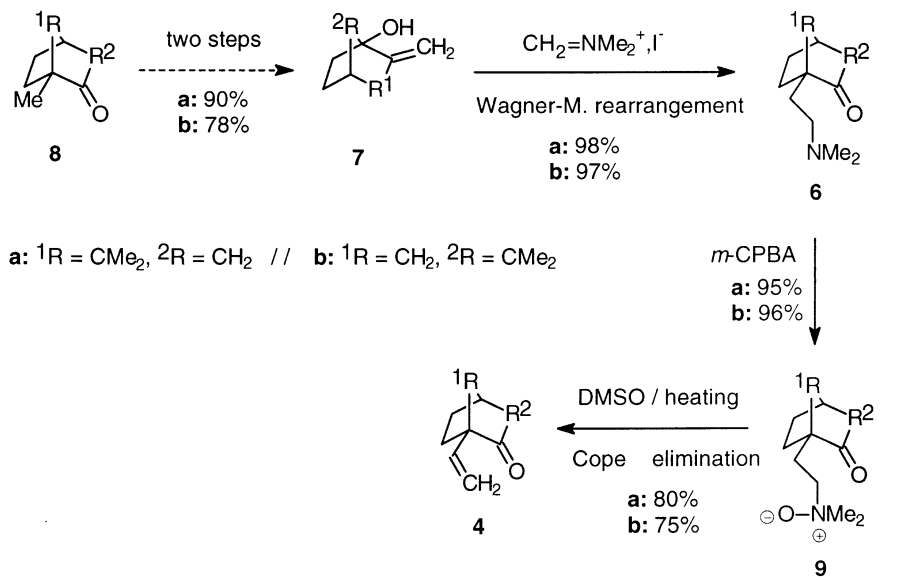
Scheme 1. Paquette's approach to taxanes.

We have now used amino ketone **6a** for the enantiospecific preparation of the taxane-intermediate, enone **4a** (Scheme 2). Thus, the treatment of **6a** with *m*-CPBA affords the corresponding *N*-oxide **9a** in excellent yield (95%).[10] Subsequent Cope elimination in DMSO gives the desired (1*S*)-10-methylenecamphor **4a** in good yield (Scheme 2) (80%).[11] The overall procedure constitutes a new straightforward route for the enantiospecific preparation of the valuable intermediate **4a** from natural (1*R*)-camphor (Scheme 2).

According to the above, we have also obtained interesting (1*R*)-10-methylenefenchone **4b**, which has been previously prepared from natural fenchone **8b** in low overall yield (20%).[12] Enone **4b**, an analogue of **4a** (3,3-dimethylated instead of 7,7-one, see Scheme 2) could be used as an intermediate in Paquette's route for the preparation of new interesting taxoids (10,10-dimethylated instead of the common 15,15-dimethylated taxanes, see Fig. 1) with unexplored and potentially interesting biological activities.[13]

The new preparation of **4b** has been realized starting from (1*S*)-7,7-dimethyl-2-methylenenorbornan-1-ol **7b**, easily obtained from commercial natural (1*R*)-fenchone **8b**.[14] Thus, when the 2-methylenenorbornan-1-ol **7b** is treated with Eschenmoser's salt, (1*R*)-10-dimethylaminomethylfenchone **6b** is obtained in ca. quantitative yield (97%).[15] Subsequent treatment with *m*-CPBA acid affords corresponding *N*-oxide **9b** (96%),[10] which is subjected to Cope elimination to obtain the desired (1*R*)-10-methylenefenchone **4b** (75%).[11]

In summary, a new enantiospecific route to 10-methylenecamphor **4a** and 10-methylenefenchone **4b** is described. The procedure takes places in five straightforward steps avoiding the use of dangerous diazomethane, which is used in the previously described procedures.[7,12] Enone **4a** is now obtained with a slightly lower overall yield than that obtained with the Fischer–Opitz procedure (67% versus 71%), but advantageously, starts from the less expensive (1*R*)-camphor instead of 10-camphorsulfonyl chloride.[7] On the other hand,



Scheme 2. New enantiospecific procedure to taxoid-intermediate 10-methylenecamphor and 10-methylenefenchone.

enone **4b** is obtained in higher yield than the previously reported protocol (54% versus 20%).[12] Enone **4b** could be used as key intermediate for the preparation of new unexplored taxoids, as analogous **4a** is used for taxol and taxusin.[6i–k] Moreover, we have enantiospecifically obtained for the first time 10-dimethylaminomethylfenchone **6b**, which can be used as interesting precursor of other C(10)–C-substituted fenchone-derived chiral sources.[8]

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10. To a solution of the appropriate amino ketone **6** in CH_2Cl_2, at −50°C, was added *m*-CPBA (57% purity, 1.6 mol equiv.). The reaction mixture was stirred at −50°C for 2 h. Excess Na_2CO_3 was added and the mixture was stirred, allowing it to warm to room temperature. After filtration and solvent evaporation, the corresponding *N*-oxide **9** was purified by column chromatography (silica gel, firstly eluting with $CHCl_3$ to remove *m*-CPBA residues and then with MeOH to elute the *N*-oxide). **9a**: 95% yield; pale-yellow gummy oil; $[\alpha]_D^{20}$ +8 (0.55, MeOH); ^1H and ^{13}C NMR, FTIR and MS spectra agree with the structure. **9b**: 96% yield, pale-yellow gummy oil; $[\alpha]_D^{20}$ −21 (0.85, MeOH); ^1H and ^{13}C NMR, FTIR and MS spectra agree with the structure.
11. A solution of the appropriate *N*-oxide **9** in dry DMSO was heated at 120°C for 4 h. After cooling to room temperature, the mixture was diluted with water and extracted with pentane. After drying and evaporation of the solvent, pure 10-methylenecamphor **4a**, or 10-methylenefenchone **4b**, was obtained. **4a**: 80% yield, pale yellow solid (for characterization data see Ref. 7). **4b**: 75% yield, colorless oil (for characterization data see Ref. 12).
12. Enone **4b** has been previously prepared from fenchone **8b**, via non-commercial 10-fenchonesulfonyl chloride, using the Fischer–Opitz method (overall yield 20%): Paquette, L. A.; Teleha, C. A.; Taylor, R. T.; Maynard, G. D.; Rogers, R. D.; Gallucci, J. C.; Springer, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 265 and references cited therein.
13. 2-Alkenyl-2-norbornanols derived from **4b** have been submitted oxy-Cope rearrangement (see Ref. 12).
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15. Amino ketone **6b** has been obtained according with the same methodology described for the preparation of analogous **6a** in Ref. 8. **6b**: 97% yield; Pale yellow solid; ^1H and ^{13}C NMR, FTIR and MS spectra agree with the structure.