SYNTHESIS OF THE A/B/C RING SYSTEM OF TAXANE DITERPENES FROM (*S*)-(+)-CARVONE

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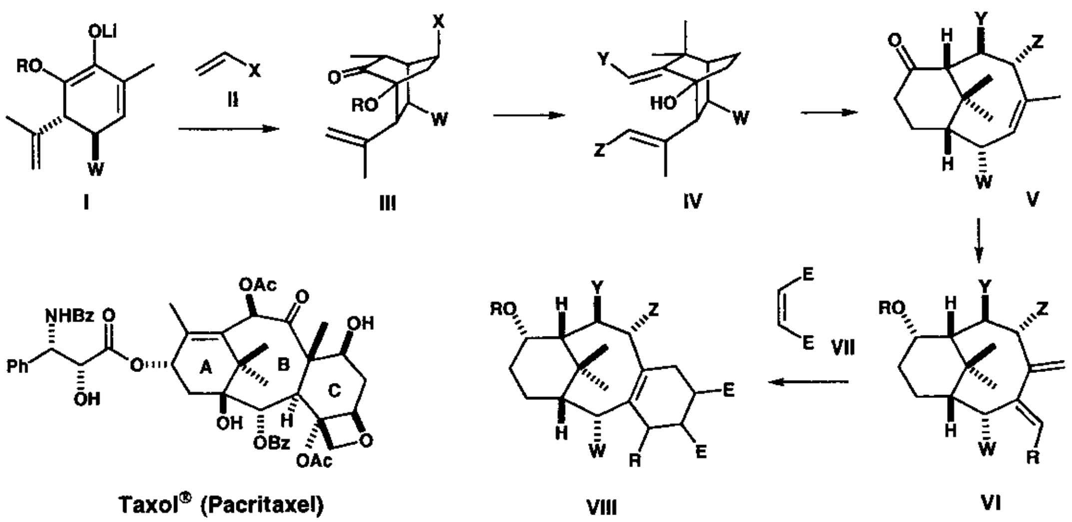
Abstract- A new route for the synthesis of the tricyclo[9.3.1.$0^{3,8}$]pentadecane skeleton, the A/B/C ring system of taxanes, *via* epoxide (**12**) from (*S*)-(+)-carvone using sequential Michael reaction followed by base-induced oxy-Cope rearrangement and Diels-Alder reaction is described.

A number of synthetic methods for the tricyclo[9.3.1.$0^{3,8}$]pentadecane derivatives have been developed in an attempt to construct the skeleton of the potent anti-tumor agent Taxol® (paclitaxel) and its analogous.[1,2] In this paper, we wish to report an alternative and efficient method for the synthesis of the optically active tricyclo[9.3.1.$0^{3,8}$]pentadecane ring system from (*s*)-(+)-carvone. Our synthetic strategy involves sequential

Figure 1



Michael reaction of enolate (**I**) with dienophile (**II**) to give bicyclo[2.2.2]octane (**III**), oxy-Cope rearrangement of hydroxy diene (**IV**) to construct the A/B ring system (**V**), and Diels-Alder reaction of diene (**VI**) with dienophile (**VII**) to form the C ring, as the key steps.

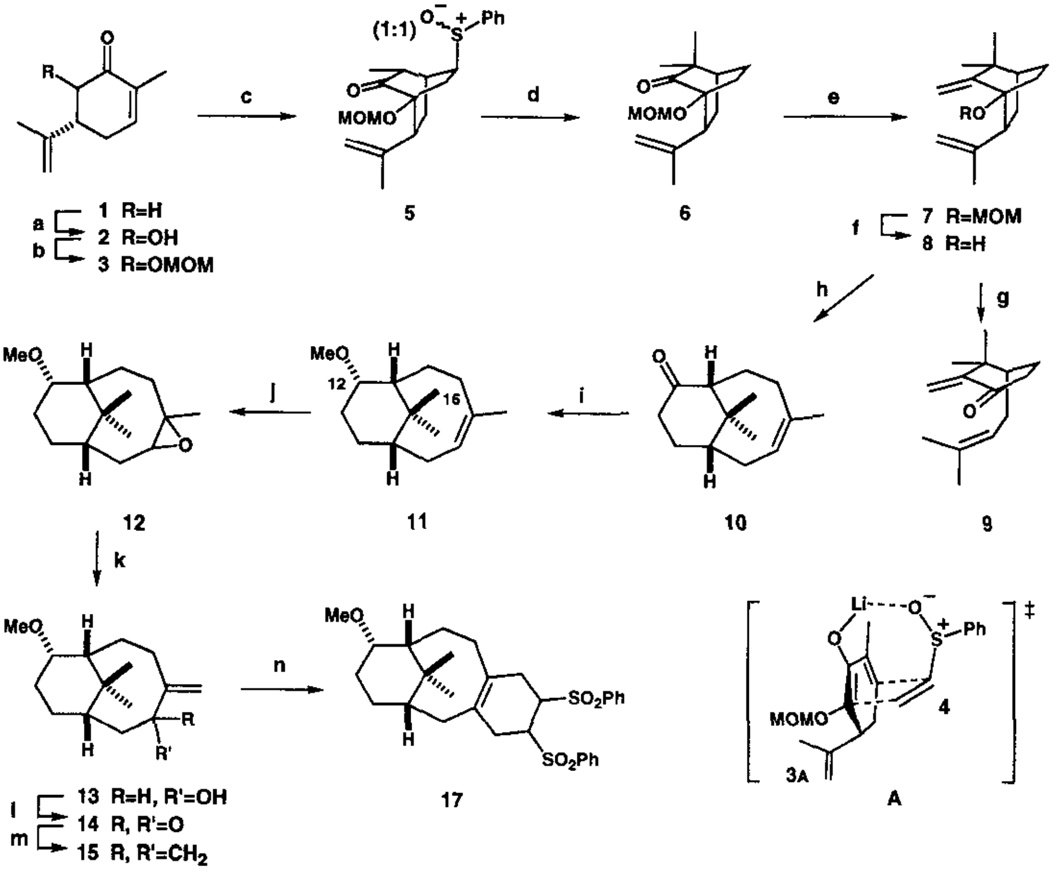
The optically active bicyclo[2.2.2]octane derivative corresponding to **III** (W=H) was synthesized by sequential Michael reaction of enone (**3**) with phenyl vinyl sulfoxide (**4**) as a dienophile. Reaction of the kinetic enolate of **3**,[3] readily prepared from (*S*)-(+)-carvone (**1**) *via* the α-hydroxy ketone (**2**), with **4** in THF-HMPA at 0°C for 1 h gave keto sulfoxide (**5**) in 82% yield (Scheme 1).[5] The configuration of the phenylsulfinyl group in **5** was estimated from the reaction mechanism. The adducts must arise *via* the preferred transition state **A** in which sulfoxide (**4**) approaches to the dienolate (**3A**) from the less hindered side with coordination between the lithium cation in **3A** and the sulfonyl oxygen of **4**. Thus obtained **5** was transformed into the 1,5-diene (**8**), the precursor of oxy-Cope rearrangement, as follows. Removal of the phenylsulfinyl group by Li-liquid ammonia reduction followed by oxidation of the resulting secondary alcohol with PDC, and C-methylation provided the dimethyl ketone (**6**), $[\alpha]_D^{25}$ -5.6° (*c* 0.6, $CHCl_3$), in 69% overall yield. Addition of trimethylsilylmethyl anion to the ketone in **6** and subsequent treatment with KH formed the exoolefin (**7**), whose methoxymethyl group was removed to the afford hydroxy diene (**8**), $[\alpha]_D^{25}$ +102.7° (*c* 0.75, $CHCl_3$), in 61% yield over three steps.

Oxy-Cope rearrangement of **8** was effected by heating at 150°C for 5 min in the presence of lithium bis(trimethylsilyl)amide in a 10:1 mixture of *o*-xylene and HMPA to give the desired bicyclo[5.3.1]undecane derivative (**10**), $[\alpha]_D^{25}$ +38.3° (*c* 0.6, $CHCl_3$), in 76% yield.[6] Lithium bis(trimethylsilyl)amide and HMPA were essential for this rearrangement; heating of **8** at 180°C in *o*-dichlorobenzene gave dienone (**9**), $[\alpha]_D^{25}$ +5.6° (*c* 0.9, $CHCl_3$), instead of **10** as a result of retro-ene reaction.

With the desired bicyclo[5.3.1]undecene derivative in hand, preparation of the diene (**15**) corresponding to **VI** (W=Y=Z=H) was conducted. Before construction of the 1,3-diene moiety, the ketone in **10** was protected as the methyl ether by a two-step sequence: 1) DIBAL reduction, and 2) methyl etherification. The configuration of the newly introduced methoxyl group in **11** was confirmed by NOE correlation between the methine proton at C-12 and the methyl proton at C-16. Epoxidation of **11** with *m*-chloroperoxybenzoic acid to afford epoxide (**12**) as a 3:10 diastereoisomeric mixture followed by treatment with lithium diisopropylamide gave allyl alcohol (**13**) in 82% yield (2 steps). Exposure of **13** to the Dess-Martin reagent resulted in oxidation of the secondary alcohol furnishing the enone (**14**), which was then converted to the diene (**15**), $[\alpha]_D^{25}$ -78.0° (*c* 0.3, $CHCl_3$), in two steps: 1) addition of trimethylsilylmethyl anion and 2) base treatment.

The construction of the C-ring was achieved by intermolecular Diels-Alder reaction of **15** with *trans*-1,2-bis-

Scheme 1



Reagents: a. 1) LDA, THF then TMSCl, -15°C, 1 h, 2) MCPBA, hexane, -15°C, 1 h, 3) 1N HCl, THF, rt, 20 min, 45% (3 steps);[4] **b**. $MeOCH_2Cl$, *i*-Pr_2NEt, CH_2Cl_2, 60%; **c**. LDA, THF-HMPA then phenyl vinyl sulfoxide (**4**), 0°C, 1 h, 82%; **d**. 1) Li, liq.NH_3-EtOH (5:1), -78°C, 30 min, 2) PDC, 4ÅMS, CH_2Cl_2, rt, 3 h, 83% (2 steps), 3) $(TMS)_2NLi$ then MeI, THF, rt, 2 h, 77%; **e**. 1) $TMSCH_2Li$, Et_2O, rt, 30 min, 82%: 2) KH, THF, rt, 80 min, 78%; **f**. MeOH-c.HCl (99:1), rt, 80 min, 95%; **g**. *i*-Pr_2NEt, *o*-dichlorobenzene, 180°C, 2 h, 56%; **h**. $(TMS)_2NLi$, *o*-xylene-HMPA (10:1), 150°C, 5 min, 76%; **i**. 1) DIBAH, CH_2Cl_2-hexane (1:1), -78°C, 10 min, 79%, 2) MeI, NaH, THF-DMF (3:1), rt, 3 h, 97%; **j**. MCPBA, Na_2HPO_4, CH_2Cl_2, 0°C, 5 min; **k**. LDA, Et_2O, rt, 2 h, 82% (2 steps); **l**. Dess-Martin reagent, AcOEt, rt, 15 min, 86%; **m**. 1) $TMSCH_2Li$, Et_2O, 5°C, 10 min, 83%, 2) *t*-BuOK, THF, rt, 15 min, 71%; **n**. *trans*-1,2-bis(phenylsulfonyl)ethylene (**16**), *o*-xylene, 100°C, 20 min, 70%.

(phenylsulfonyl)ethylene (**16**) as the dienophile. The mixture of **15** and **16** in *o*-xylene was heated at 100°C for 20 min and the cyclization then took place smoothly to form the desired tricyclo[9.3.1.$0^{3,8}$]pentadecane ring system (**17**) in 70% yield.[7, 8]

Thus, the synthesis for the A/B/C ring system of taxane diterpenes was accomplished from (S)-(+)-carvone as the chiral starting material.[9] Further investigation of the synthesis of highly functionalized tricyclo[9.3.1.$0^{3,8}$]-pentadecane derivatives by this strategy is now in progress in this laboratory.

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