Pergamon

Tetrahedron Letters 40 (1999) 4881–4884

TETRAHEDRON LETTERS

A New Carvone Based Construction of the Ring-A of Taxoids

Goverdhan Mehta,* Shital K. Chattopadhyay and Jayant D. Umarye

Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

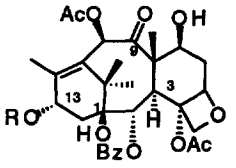
Received 1 April 1999; accepted 6 May 1999

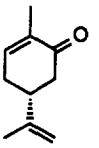
Abstract: A synthesis of the fully functionalized A-ring of taxoids from the commercially available monoterpenic chiron R-carvone is outlined. In this approach, regio- and stereoselective restructuring of alkyl substituents and functionalities is effected on the periphery while retaining the six membered core of carvone.

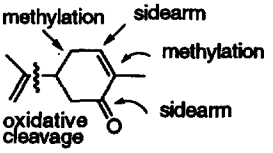
Key words: Taxoids; Barbier reactions; allylation

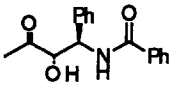
Although, the complex and synthetically challenging natural product paclitaxel **1** has yielded to six total syntheses in as many years,[1] interest in exploring newer avenues to construct whole or part of its functionally embellished tetracyclic frame continues to persist worldwide.[2,3] Indeed, few molecules in recent years have stirred as much imagination and activity among synthetic chemists as **1**, primarily because of its framework complexity, clinical use as a powerful anti-cancer drug and possibility of discovering more potent and possibly structurally less complex synthetic analogues.[3] While some have taken to the marathon task of total synthesis of **1**, many have pursued a less ambitious but no less creative approach and confined their efforts to introducing a new idea or methodology by demonstrating the model construction of certain segments of **1**, like one or more of the A-D rings with appropriate functionalization.

We became interested in exploring a new approach to the six-membered A-ring of paclitaxel **1** from the cheap and commercially available monoterpenic chiron (-)-carvone **2**. Although there are reports galore[4] of approaches to ring A of **1**, only one has emanated from carvone.[5] We envisaged a new, simple and straightforward approach to







1 R= 

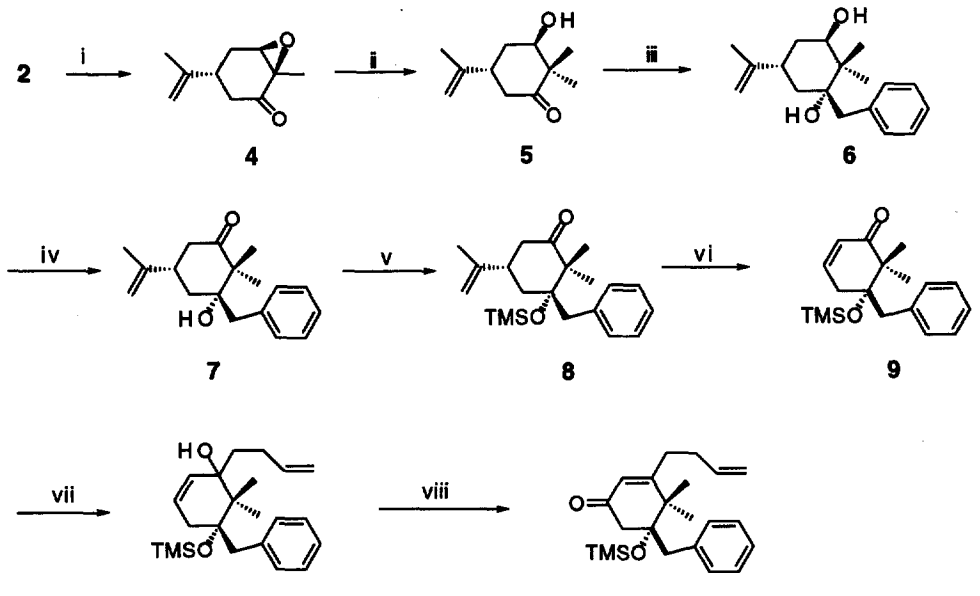
2

3

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00902-8

the A-ring of **1** from carvone **2** in which its six-membered ring is retained as such but the alkyl substituents and functionalization on its periphery are readjusted to generate the requisite framework. The key elements of this restructuring plan are displayed in structure **3**. In this communication, attainment of the A-ring intermediates through the restructuring of the carvone nucleus is described; a notable feature being the control of C_1 and C_{13} (taxane numbering) relative stereochemistry through an intramolecular process.

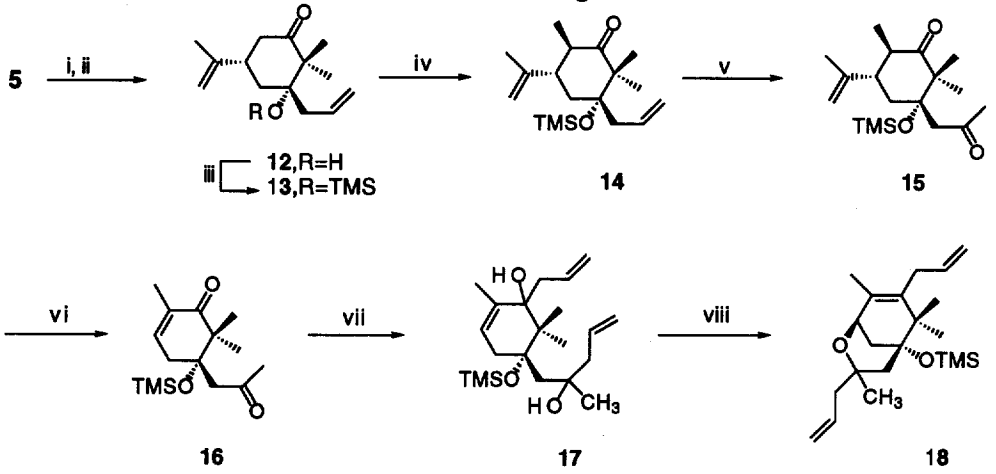
Our synthetic approach commenced from the cheaper, more abundant R-(-)-carvone **2**, although it will give the antipodal series compared to the natural product. However, this was not considered a limiting factor as carvone is readily available in both the enantiomeric forms. (-)-Carvone **2** was readily elaborated to the hydroxy-ketone **5** *via* a two step sequence involving reductive methylation of the derived α,β-epoxyketone **4** as described previously.[6] Barbier reaction on **5** with benzyl bromide led to the diol **6**[7] as a single diastereomer with the isopropenyl group acting as a chiral director and addition taking place from the face opposite to it. Oxidation of **6** with TPAP furnished the hydroxy-ketone **7** in which the tertiary hydroxyl group was protected as TMS-ether **8**.[7] Oxidative removal of the isopropenyl group in **8** *via* Criegee rearrangement[8] led to the enone **9**.[7] Barbier reaction of butenyl bromide with **9** proceeded satisfactorily to furnish the allylic alcohol **10**.[7] PCC mediated oxidative allylic rearrangement in **10** led to the enone **11**,[7] Scheme 1. Acquisition of **11**, having the requisite features but lacking the C_{12} methyl group, constituted an encouraging model study and set the stage for the complete construction of the A-ring of taxanes.



Scheme 1:Reagents and conditions : (i) H_2O_2, NaOH, 0°C, 98%. (ii) Li, liq.NH_3, MeI, 60%. (iii) BnBr, Li, THF,)))) , 35%. (iv) TPAP, NMMO, 4Å mol. sieves, CH_2Cl_2, r.t., 86%. (v) TMS-imidazole, cat.TBAF, DMF, r.t., 91%. (vi) O_3, CH_2Cl_2-MeOH, -78°C to r.t., then Ac_2O, Et_3N, DMAP, benzene, Δ, 40%. (vii) 4-bromo-1-butene, Li, THF,))))), 30 min., 79%. (viii) PCC, CH_2Cl_2, r.t., 81%.

Allylation of hydroxy-ketone **5** with allyl bromide in the presence of Zn, under sonication, led to a diol which was directly oxidised to the hydroxy-ketone **12**[7] with TPAP. Protection of the tertiary hydroxyl group in **12** led to the TMS-ether **13**.[7] Base mediated α-methylation in **13** was achieved after considerable trial and error and the desired methyl group was efficiently introduced eventually to yield **14** as a single diastereomer, Scheme 2. Palladium catalysed regioselective Wacker oxidation in **14** gave the methylketone **15** and set the stage for the removal of the isopropenyl group *via* ozonolysis and Criegee rearrangement.[8] Thus, **15** furnished enone **16**[7], which was ready for the alkylative transposition.[9] Reaction of allylmagnesium bromide with **16** gave the double addition product **17** and quite remarkably it turned out to be a single diastereomer, possibly a consequence of the chelation effect of the -OTMS group. Quite unexpectedly, PCC oxidation of **17** furnished **18** through allylic transposition involving the participation of the side chain hydroxyl group, Scheme 2. Thus, no formal oxidation is involved with PCC but instead the initially formed allylic chromate ester is displaced in an intramolecular SN2' like process, in consonance with the proposed mechanism[9] for the PCC mediated oxidative allylic transpositions. It is to be noted that the formation of **18** is not a simple acid catalysed intramolecular etherification process as exposure of **17** to acids only led to intractable products through extensive dehydration of the two tertiary hydroxyl functionalities.

Formation of **18** was a pleasing outcome as it secured the correct relative stereochemistry of the secondary and the tertiary hydroxyl groups (see C_1 and C_{13} in paclitaxel **1**). It is interesting to note that in the beginning of our synthesis, the C_1 (taxane numbering) centre is created under the chiral direction of the isopropenyl group (**5** ->**12**) which is subsequently discarded and in the end (**17**->**18**), C_1 returns the favour and directs the recreation of C_{13} with the desired stereochemistry. In **18**, all the elements of ring-A that were contemplated are present. Our further plans are aimed at closing the olefin bearing side arms in **18** and related compounds through ring-closure metathesis (RCM) reaction[10] to construct the B-ring.



Scheme 2: Reagents and conditions : (i) allyl bromide, Zn, THF,)))), 90%. (ii) TPAP, NMMO, 4Å mol. sieves, CH_2Cl_2, 88%. (iii) TMS-imidazole, cat.TBAF, DMF, 1.5h, 95%. (iv) KH(10eq), MeI (15eq), THF, -10°C, 12h, 95%. (v) $PdCl_2$, CuCl, O_2, DMF-H_2O, 48h, 60%. (vi) O_3, $Cu(OAc)_2$, $FeSO_4$, CH_2Cl_2-MeOH, -78°C, 60%. (vii) allylmagnesium bromide (excess) , ether, 0°C, 65%. (viii) PCC, NaOAc, r.t., 2h, 90%.

In summary, we have outlined a flexible and straightforward protocol, complete with regio- and stereocontrol, for accessing the A-ring of taxoids from the readily available chiron R-(-)-carvone **2**.

Acknowledgements: We thank Jawaharlal Nehru Centre for Advanced Scientific Research, Bangalore, for supporting this research project and for the award of a Research Associateship to SKC. One of us (JDU) thanks CSIR for a Research fellowship.

References

[1] (a) Nicolaou KC, Yang Z, Liu JJ, Ueno H, Nantermet PG, Guy RK, Clalborne CF, Renaud J, Couladouros EA, Paulvannan K, Sorensen EJ. *Nature* ,**1994**, *367*, 630. (b) Holton RA, Somoza C, Kim H-B, Liang F, Biediger RJ, Boatman PD, Shindo M, Smith CC, Kim S, Nadizadeh H, Suzuki Y, Tao C, Vu P, Tang S, Zhang P, Murthi KK, Gentile LN, Liu JH. *J. Am. Chem. Soc.*, **1994**, *116*, 1597; *idem.*, **1994**, *116*, 1599. (c) Masters JJ, Link JT, Synder LB, Young WB, Danishefsky SJ. *Angew. Chem., Int. Ed. Engl.*, **1995**, *34*, 1723. (d) Wender PA, Badham NF, Conway SP, Floreancig PE, Glass TE, Houze JB, Krauss NE, Lee D, Marquess DG, McGrane PL, Meng W, Natchus MG, Shuker AJ, Shutton JC, Taylor RE. *J. Am. Chem. Soc.*, **1997**, *119*, 2757. (e) Shiina I, Iwadare H, Sakoh H, Hashigawa M, Tani Y, Mukaiyama T. *Chem. Lett.*, **1998**, 1. (f) Morihira K, Hara R, Kawahara S, Nishimori T, Nakamura N, Kusama H, Kuwajima I. *J. Am. Chem. Soc.*, **1998**, *120*, 12980.

[2] Recent review on some approaches to taxoids: Mehta G, Singh VK. *Chem. Rev.*, **1999**, *99*, 881.

[3] Recent review: Nicolaou KC, Dai W-M, Guy RK. *Angew. Chem., Int. Ed. Engl.*, **1994**, *33*, 15.

[4] (a) Wei C-Q, Jiang X-R, Ding Y, *Tetrahedron*, **1998**, *54*, 12623. (b) Toivola RJ, Koskinen AMP, *Synlett*, **1996**, 1159. (c) Takahashi T, Iwamoto H. *Tetrahedron Lett.*, **1997**,*38*, 2483. (d) Yadav JS, Srinivas D. *Tetrahedron Lett.*, **1997**, *38*, 7789. (e) Winkler JD, Bhattacharya SK, Liotta F, Batey RA, Heffernan GD, Cladingboel DE, Kelly RC. *Tetrahedron Lett.*, **1995**, *36*, 2211. (f) Funk RL, Yost III , KJ. *J. Org. Chem.*, **1996**, *61*, 2598. (g) Taber DF, Walter R, Meagley RP. *J. Org. Chem.*, **1994**, *59*, 6014. (h) Crich D, Crich JZ. *Tetrahedron Lett.*, **1994**, *35*, 2469. (i) Doi T, Robertson J, Stork G, Yamashita A. *Tetrahedron Lett.*, **1994**, *35*, 1481.

[5] (a) Srikrishna A, Reddy TJ, Praveen Kumar P. *Chem. Commun.*, **1996**, 1369. (b) Srikrishna A, Reddy TJ, Praveen Kumar P. *J. Chem. Soc., Perkin Trans. 1*, **1998**, 3143.

[6] McChesney JD, Thompson TN. *J. Org. Chem.*, **1985**, *50*, 3473.

[7] All new compounds were fully characterised on the basis of complementary spectral (IR, ^{1}H and ^{13}C NMR, Mass) data. Selected data for the key compounds: **17** : $[\alpha]_D$ -41.57° ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.85-5.60 (2H, m, 2x C<u>H</u>=CH_2), 5.15 (1H, m, C<u>H</u>=C-Me), 4.90-4.80 (4H, m, 2x CH=C<u>H_2</u>), 2.30-2.20 (m, 2H), 2.10-2.09 (2H, m), 1.91 (1H, d, J=15.3 Hz), 1.71 (1H, d, J=15.3 Hz), 1.51 (3H, s, =C-<u>Me</u>), 1.42 (2H, m), 1.16 (3H, s), 1.08 (3H, s), 0.99 (3H, s), 0.25 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 137.1, 136.0, 135.2, 122.9, 117.8, 117.5, 83.5, 77.1, 72.7, 47.5, 46.6, 44.6, 42.2, 36.2, 29.9, 21.5, 19.6, 17.1, 3.6. **18**: $[\alpha]_D$ -96.87° ($CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) : δ 5.66-5.60 (2H, m, 2x C<u>H</u>=CH_2), 4.93-4.80 (4H, m, 2x C=C<u>H_2</u>), 3.89 (1H, t, J=3.5Hz), 2.82 (2H, dq, J=15.3 & 6.5 Hz), 2.42 (1H, dd, J=14.1 & 6.5 Hz), 2.23 (1H, dd, J=14.7 & 2.1 Hz), 2.16-2.09 (2H, m), 1.87 (1H, dd, J=11.9 & 2.9 Hz), 1.72 (3H, s), 1.58 (1H, d, J=14.7 Hz), 1.20 (3H, s), 1.05 (3H, s), 0.98 (3H, s), 0.20 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) : δ 138.6, 136.2, 135.6, 129.1, 116.9, 115.5, 74.9, 74.5, 74.3, 46.2, 45.7, 45.0, 36.6, 33.6, 32.9, 23.8, 19.9, 18.1, 2.58; Mass: m/z 307 (M^+-C_3H_5).

[8] (a).Schreiber SL, Liew W-F. *Tetrahedron Lett.*, **1983**, *24*, 2363. (b) Meulemans TM, Stork GA, Jansen BJM, de Groot A. *Tetrahedron Lett.*, **1998**, *39*, 6565 .

[9] Dauben WG, Michno DM. *J. Org. Chem.*, **1977**, *42*, 682.

[10] Grubbs RH , Chang S. *Tetrahedron*, **1998**, *54*, 4413.