Pergamon

Tetrahedron Letters, Vol. 38, No. 15, pp. 2759-2762, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00463-2

Synthesis of Bicyclo[9.3.1]pentadecane Derivatives, Interesting Intermediates for the Preparation of Taxuspine U and Related Diterpenoids[1]

Federico Corelli,* Donata Dei,[2] Maria Menichincheri,[#] James P. Snyder,[†] and Maurizio Botta*

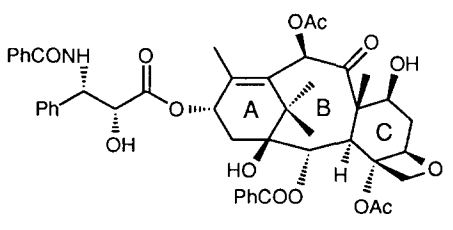
Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Banchi di Sotto 55, 53100 Siena, Italy

[#]Chemistry Department, Pharmacia & Upjohn, Via Giovanni XXIII, 20014 Nerviano, Milano, Italy

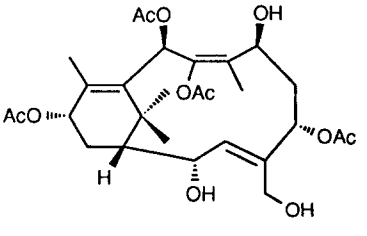
[†]Department of Chemistry, Emory University, Atlanta, GA 30322, USA

Abstract: The synthesis of regioisomeric bicyclo[9.3.1]pentadecane-3-one derivatives **1** and **2**, interesting synthons for the preparation of novel diterpenoids, has been accomplished through an approach that entails as a key step the formation of a twelve-membered ring by an unprecedented intramolecular Dieckmann cyclisation. © 1997 Elsevier Science Ltd.

The remarkable therapeutic potential and challenging structural complexity of taxane diterpenoids have stimulated worldwide enormous synthetic efforts which have culminated in three different total syntheses of paclitaxel (Taxol®).[3] The synthetic studies may play a very important role in the search for paclitaxel analogues or second-round drug candidates and, accordingly, numerous approaches to the tricyclic core of paclitaxel have been reported.[4]



paclitaxel

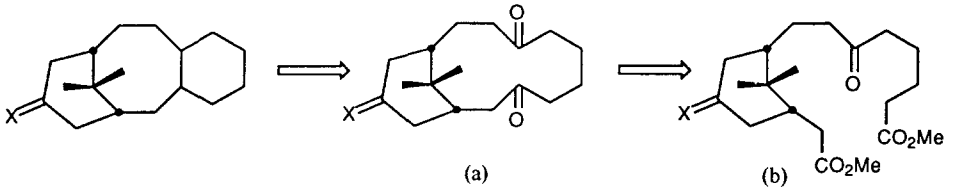


taxuspine U

In the course of our investigations on new analogues of paclitaxel,[5] we sought a different approach to the A/B/C ring system of diterpenoid taxanes. According to our synthetic strategy (Scheme 1), the B and C rings are envisioned to arise from titanium-mediated[6] transannular cyclisation[7] of a macrocyclic diketone (a), in turn assembled by Dieckmann reaction of an appropriate diester (b). Very recently, three new taxane and related

diterpenoids were isolated from the stems of the Japanese yew *Taxus cuspidata*.[8] Among these, taxuspine U is a very rare bicyclic diterpenoid which could be isolated in only 0.000017% yield. Considering the intriguing structure and possible pharmacological interest of taxuspine U, we describe here our results concerning the synthesis of bicyclo[9.3.1]pentadecane-3-one-4-carboxylic acid methyl ester **1** (along with its regioisomer **2**) a precursor of the diketone (a) and interesting synthon for the preparation of taxuspine U and related diterpenoids.

Scheme 1

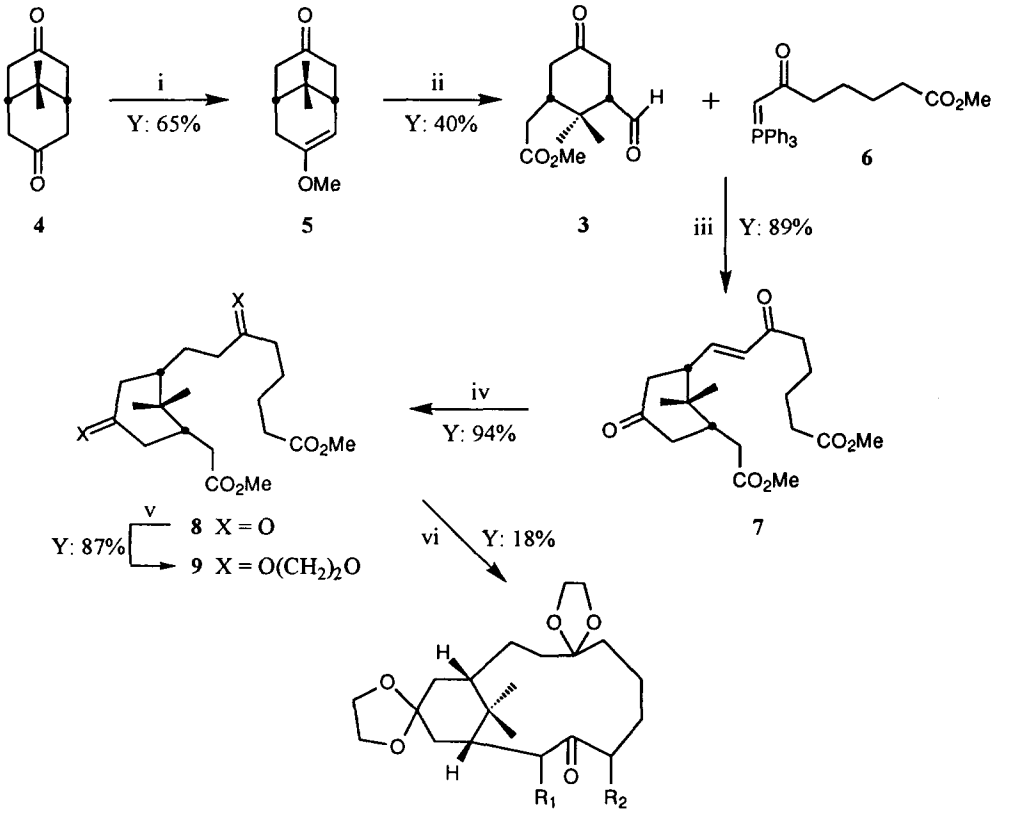


The synthesis began with the preparation of the keto aldehyde **3** (Scheme 2).[9] The readily accessible diketone **4**[10] was transformed into the monoenol ether **5** by treatment with LDA (1.1 molar equivalents) and methyl triflate in 65% yield after chromatographic purification. Subsequent cleavage of the double bond with $OsO_4/NaIO_4$ gave **3** in moderate yield (40%). Wadsworth-Emmons condensation of **3** with ylide **6**[11] afforded the unsaturated ketone **7** which was in turn subjected to catalytic hydrogenation in the presence of 10% Pd/C as the catalyst to give **8**. Protection of the ketone functions under standard conditions (ethylene glycol, camphorsulphonic acid, refluxing toluene) provided the diester **9**[12] (73% overall yield from **3**).

With compound **9** in our hands, we started to explore the possibility of cyclisation *via* several procedures reported in the literature for the Dieckmann reaction.[13] It is well known that this intramolecular reaction usually fails to afford nine- to twelve-membered rings because of the unfavoured entropy involved, but such results basically refer to linear, completely flexible, diesters.[14] In compound **9** the ester groups lie at the end of two chains linked to a cyclohexane ring in a 1,3-*cis* relative disposition, and we reasoned that this steric constraint might prevail, at least in part, over the unfavourable entropic factor involved in the intramolecular cyclisation. After several unsuccessful attempts to promote the ring closure of **9** under a variety of conditions with sodium hydride or potassium *tert*-butoxide, we were delighted to find that, upon treatment with sodium bis(trimethylsilyl)amide in refluxing THF under high-dilution conditions,[15] **9** smoothly cyclised to provide the bicyclo[9.3.1]pentadecane-3-one-4-carboxylic acid methyl ester **1** as an unseparable mixture (18% yield) with its regioisomer **2**.[16,17] The structure of **1** and **2** has been assigned on the basis of their spectroscopic (^1H NMR, ^{13}C NMR, MS) data. In particular, the 200 MHz ^1H NMR spectrum of this mixture shows two singlets at 3.71 and 3.78 ppm, in the ratio 3:1 and integrating for a total of three protons, attributable to the methoxycarbonyl group of the two isomers. Consistently, in the ^{13}C NMR spectrum three signals are present which can be attributed to three carbonyl groups. Finally, the EI-mass spectrum shows a peak at m/z 425 corresponding to the $(M+1)^+$ ion. It is interesting to point out that no evidence of the formation of dimeric ketone(s) has been obtained. No attempt has been made so far to separate isomers **1** and **2** by preparative HPLC, in view of the possibility of converting them into the same compound by decarbalkoxylation *en route* to a ketone such as (a) in Scheme 1.

In conclusion, we have described here the preparation of the bicyclo[9.3.1]pentadecane-3-one derivatives **1** and **2** through a practical synthesis (nine steps from commercially available starting materials) that encompasses the unprecedented Dieckmann cyclisation to a twelve-membered ring. Owing to the possibility of further optimizing some of the reactions involved, including the Dieckmann reaction itself, this synthetic sequence could allow the preparation in reasonable yield of the target bicyclic compounds **1** and **2**, versatile synthons to obtain new diterpenoid compounds.

Scheme 2



Reagents: (i) LDA, CF_3SO_2OMe, THF, -78 °C to RT; (ii) OsO_4 (cat.), $NaIO_4$, Et_2O, H_2O; (iii) toluene, 100 °C; (iv) H_2 (1 atm.), 10% Pd/C, AcOEt; (v) ethylene glycol, CSA, toluene, reflux; (vi) $NaN(SiMe_3)_2$, THF, reflux.

Acknowledgments. We are grateful to the Italian MURST (40% and 60% funds) and Pharmacia & Upjohn (Milano) for financial support of this research. Two of us (M.B. and J.P.S.) wish to thank for a collaborative research grant the NATO International Scientific Exchange Programme "Bioactive Conformation and Design Mimics for the Anticancer Agent Taxol" [NATO Reference: SA.5-2-05(CRG. 960711)]. We thank Dr. N. Mongelli, Pharmacia & Upjohn, for helpful discussions.

REFERENCES AND NOTES

1. Taken in part from the Ph.D. Thesis of D.D., University of Siena, 1996.
2. Present address: L. Molteni & C. S.p.A. dei F.lli Alitti, S.S. Tosco-Granatieri, 50018 Scandicci (FI), Italy.
3. (a) Holton, R.A.; Somoza, C.; Kim, H.B.; Liang, F.; Biediger, R.J.; Boatman, P.D.; Shido, M.; Smith, C.C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K.K.; Gentile, L.N.; Liu, J.H. *J. Am. Chem. Soc.* **1994**, *116*, 1597. (b) Holton, R.A.; Somoza, C.; Kim, H.B.; Liang, F.; Biediger, R.J.; Boatman, P.D.; Shido, M.; Smith, C.C.; Kim, S.; Nadizadeh, H.; Suzuki, Y.; Tao, C.; Vu, P.; Tang, S.; Zhang, P.; Murthi, K.K.; Gentile, L.N.; Liu, J.H. *ibid.* **1994**, *116*, 1599. (c) Nicolaou, K.C.; Yang, Z.; Liu, J.J.; Ueno, H.; Nantermet, P.G.; Guy, R.K.; Claireborne, C.F.; Renaud, J.; Couladouros, E.A.; Paulvannan, K.; Sorensen, E.J. *Nature* **1994**, *367*, 630. (d) Nicolaou, K.C.; Nantermet, P.G.; Ueno, H.; Guy, R.K.; Couladouros, E.A.; Sorensen, E.J. *J. Am. Chem. Soc.* **1995**, *117*, 624. (e) Nicolaou, K.C.; Liu, J.J.; Yang, Z.; Ueno, H.; Sorensen, E.J.; Claireborne, C.F.; Guy, R.K.; Hwang, C.K.; Nakada, M.; Nantermet, P.G. *ibid.* **1995**, *117*, 634. (f) Nicolaou, K.C.; Yang, Z.; Liu, J.J.; Nantermet, P.G.; Claireborne, C.F.; Renaud, J.; Guy, R.K.; Shibayama, K. *ibid.* **1995**, *117*, 645. (g) Nicolaou, K.C.; Ueno, H.; Liu, J.J.; Nantermet, P.G.; Yang, Z.; Renaud, J.; Paulvannan, K.; Chadha, R. *ibid.* **1995**, *117*, 653. (h) Danishefsky, S.J.; Masters, J.J.; Young, W.B.; Link, J.T.; Snyder, L.B.; Magee, T.V.; Yung, B.K.; Isaacs, R.C.A.; Bornmann, W.G.; Alaimo, C.A.; Coburn, C.A.; Di Grandi, M.J. *ibid.* **1996**, *118*, 2843.
4. For selected recent contributions, see: (a) Guénard, D.; Guéritte-Voegelein, F.; Potier, P. *Acc. Chem. Res.* **1993**, *26*, 160. (b) Nicolaou, K.C.; Dai, W.-M.; Guy, R.K. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 15. (c) Boa, A.N.; Jenkins, P.R.; Lawrence, N.J. *Contemporary Organic Synthesis* **1994**, *1*, 47.
5. Menichincheri, M.; Botta, M.; Ceccarelli, W.; Ciomei, M.; Corelli, F.; D'Anello, M.; Fusar-Bassini, D.; Mongelli, N.; Pesenti, E.; Pinciroli, V.; Tafi, A.; Vanotti, E. *Med. Chem. Res.* **1995**, *5*, 534.
6. Titanium-mediated reductive couplings of dicarbonyl compounds have been frequently employed for the synthesis of four- to eighteen-membered cycloalkenes. For selected references, see: McMurry, J.E. *Chem. Rev.* **1989**, *89*, 1513.
7. Previous attempts to prepare the tricyclic core of taxanes by Lewis acid-induced transannular cyclisation of the putative biogenetic precursors *E,E*-verticillene and verticillol were unsuccessful. See: Begley, M.J.; Jackson, C.B.; Pattenden, G. *Tetrahedron* **1990**, *46*, 4907 and references cited therein.
8. Hosoyama, H.; Inubushi, A.; Katsui, T.; Shigemori, H.; Kobayashi, J. *Tetrahedron* **1996**, *41*, 13145.
9. The structures of the new compounds were determined by EI-MS and ^{1}H NMR spectroscopy. All the new compounds gave satisfactory (±0.4% of the theoretical values) elementary analyses.
10. Aranola, G.; Bernassau, J.-M.; Fetizon, M.; Hanna, I. *J. Org. Chem.* **1985**, *50*, 1156.
11. Ylide **6** was prepared by reaction of methylenetriphenylphosphorane (2 molar equivalents) with the acid chloride of adipic acid monomethyl ester in THF at -78 °C. The purification of **6** proved to be troublesome and the pure ylide was obtained as a white crystalline solid (18-20% yield, m.p. 98-99 °C) after several recrystallizations from diethyl ether.
12. Colourless crystals, m.p. 70-72 °C. EI-MS: *m/z* 448 (M^+). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.66 (s, 3H); 0.97 (s, 3H); 1.29-1.45 (m, 7H); 1.55-1.72 (m, 8H); 1.97 (d, 2H, J = 10 Hz); 2.32 (t, 2H, J = 6 Hz); 2.55 (d, 1H, J = 10 Hz); 3.67 (s, 3H); 3.68 (s, 3H); 3.93 (s, 8H).
13. Davis, B.R.; Garratt, P.J. In *Comprehensive Organic Synthesis*; *V. 2*, Trost, B.M., Fleming, I, Eds.; Pergamon Press: Oxford, England, 1991; pp 795-863.
14. Schaefer, J.P.; Bloomfield, J.J. *Organic Reactions, V. 15*; Wiley: New York, 1967; pp 1-203.
15. Terunuma, D.; Motegi, M.; Tsuda, M.; Sawada, T.; Nozawa, H.; Nohira, H. *J. Org. Chem.* **1987**, *52*, 1630.
16. Experimental procedure for Dieckmann cyclisation of **9** (adapted from ref. 14): A solution of **9** (136 mg, 0.3 mmol) in dry THF (200 mL) was added to a gently refluxing solution of sodium bis(trimethylsilyl)amide (715 mg, 3.9 mmol) in dry THF (60 mL) over a period of 7 h, with vigorous stirring under a nitrogen atmosphere. After the addition was complete, the mixture was refluxed for an additional hour and then cooled to 0-5 °C. Acetic acid was added to the mixture until pH 7, and the solution was concentrated under reduced pressure, diluted with ethyl acetate (50 mL), washed with brine and dried. Evaporation of the solvent gave a residue which was purified by column chromatography on silica gel to afford a mixture of **1** and **2** (24 mg, 18% yield) as a colourless oil. EI-MS: *m/z* 425 $(M+1)^+$. ^{1}H NMR (200 MHz, $CDCl_3$): major isomer, δ 0.70 (s, 3H); 0.95 (s, 3H); 1.25-1.55 (m, 8H); 1.60-1.92 (m, 8H); 1.98 (d, 1H); 2.62 (d, 1H); 3.71 (s, 3+1H); 3.95 (s, 8H); minor isomer, δ 0.70 (s); 0.95 (s); 1.25-1.55 (m); 1.60-1.92 (m); 2.25-2.51 (m); 3.42 (t); 3.78 (s). ^{13}C NMR (50 MHz, $CDCl_3$): δ 204.7 (ketone carbonyl); 173.8 and 170.1 (ester carbonyls); 111.5 and 107.9 (ketal O-C-O).
17. This reaction has not yet been optimized as 10-12% of the starting diester **9** was consistently recovered.

(*Received in UK* 15 *January* 1997; *accepted* 7 *March* 1997)