Pergamon

Tetrahedron Letters, Vol. 37, No. 47, pp. 8459-8462, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01947-8

A Scalemic Synthesis of the Scopadulcic Acid Skeleton. I: An Efficient γ-Alkylation at C-9 in Abietane Framework and Subsequent Aldol Reaction

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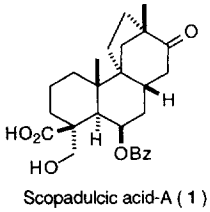
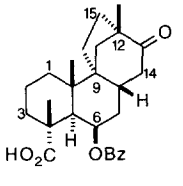
Abstract: The first example of a carbon-carbon bond formation at C-9 in the abietane framework via a highly practical γ-alkylation of the enone **6** is reported. Attempted intra-molecular aldol reaction of the derived enone aldehyde **13** gave exclusively the undesired product **14**. However, the 12-methyl enone aldehyde **17** gave a trace of the desired aldol **19**, bond formation at C-7 still being the major pathway. Copyright © 1996 Elsevier Science Ltd

Scopadulcic acids A (**1**) and B (**2**) were isolated from the Paraguan plant *Scoparia dulcis L* by Hayashi and co-workers in 1987.[1] The challenging structural complexity inherent in this family of tetracyclic diterpenes coupled with their interesting biological effects[2] makes them worthy synthetic targets. Overman[3a] and Ziegler[3b] have completed total syntheses of these compounds in their racemic form and Meyers[3c] has reported a non-racemic approach to an A-ring aromatized model compound. The Overman group has also completed an enantioselective synthesis of scopadulcic acid A recently.[3d] In this and in the following paper, we describe an efficient protocol for a *chiral, non-racemic synthesis* of the tetracyclic framework typical of scopadulcic acids.

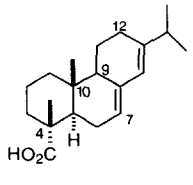
During a program directed towards discovering non-nucleoside anti-viral agents, we became interested in scopadulcic acid-B (SA-B) due to its reported inhibitory effects at the early stages of herpes virus replication. We set ourselves the goal of developing a medicinal chemistry approach to the tetracyclic framework of the natural product that would allow us to study structure-activity relationships (SAR) enroute to the final target.[4] Struck by the structural similarity between SA-B and abietic acid **3**, especially at carbons 4, 5 and 10, we envisioned the synthesis of SA-B as a problem in constructing a two carbon bridge from C-9 to C-12 in the abietane scaffold. An account of successful carbon-carbon bond formation at the sterically conjested C-9 and our attempts to induce ring closure at C-12 follows.



Scopadulcic acid-A (**1**)



Scopadulcic acid-B (**2**)

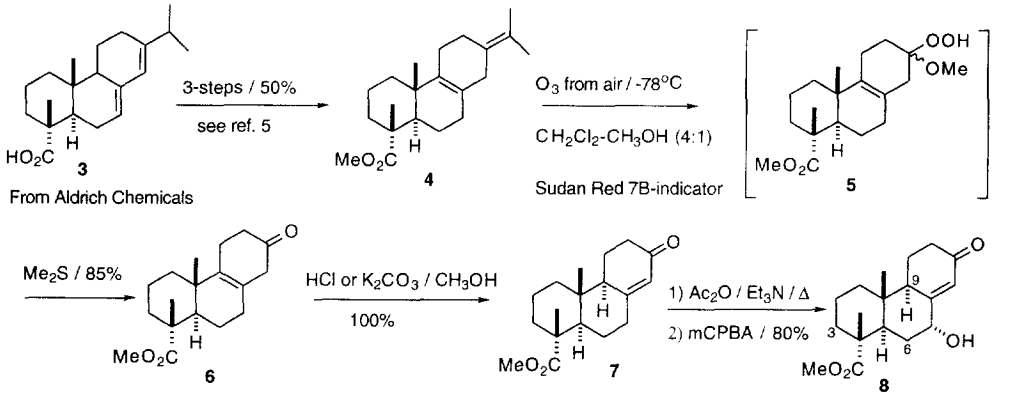


Abietic acid (**3**)

The conversion of abietic acid to the tricyclic enones **6** and **7** has been reported previously.[5] Although the synthesis of the tricyclic diene **4** can be carried out on multi-gram scale, its ozonolysis is not as slow as originally claimed. We found that the *inclusion of methanol as a co-solvent is essential during the ozonolysis of the skipped diene 4;* under these conditions, the unstable ozonide is trapped as a stable methoxy hydroperoxide intermediate (**5**) which upon reductive work-up with Me_2S furnishes the skipped enone **6** in excellent yield. Treatment with

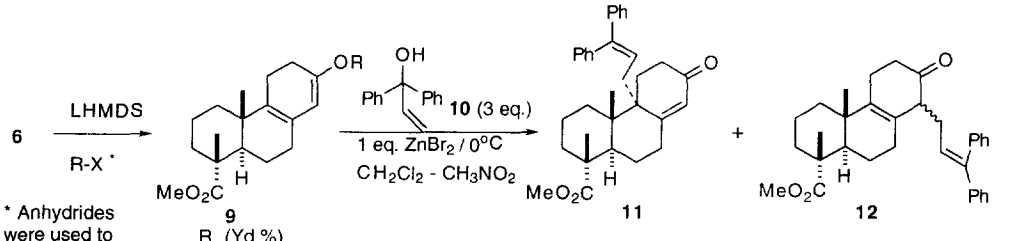
acid or base leads to the conjugated enone **7** which was converted to the 7α-hydroxy enone **8** by the method of Kirk.[6]

Scheme 1: Large Scale Synthesis of Abietenones 6 and 7



In early attempts, we anchored a number of electrophilic two-carbon pieces to the 7α-hydroxy group in **8**, but were unable to effect bond formation at the neopentyl C-9 center.[7] We then turned our attention to *intermolecular alkylation* of the skipped enone **6**. γ-Alkylation of simple dienyl silyl ethers by carbocation species has been described by Fleming.[8] We decided to explore the γ-alkylation of homonuclear dienes **9**, readily accessible from **6**, by various acetaldehyde carbocation synthons.

Scheme 2: Selective γ-Alkylation of Skipped Enone 6



* Anhydrides were used to prepare the dienyl esters.

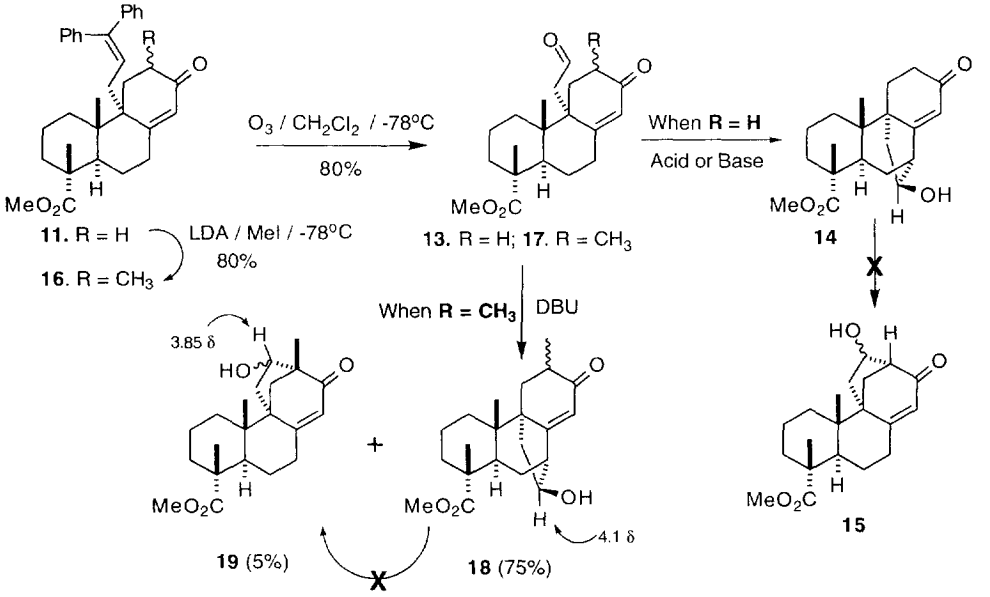
9
R (Yd.%)
a) TBDMS (90%)
b) $SiPh_3$ (70%)
c) $COCH_3$ (50%)
d) $COCMe_3$ (100%)
e) $COCPh_3$ (90%)

Diene	11	12 (isolated yd.)
9a	5%	-
9b	15%	50%
9c	25%	50%
9d	45%	45%
9e	65%	30%

Ethylene oxide, bromoacetaldehyde dimethyl acetal, dimethylallyl bromide etc.were found to lack the reactivity needed to alkylate the neopentyl carbon in diene **9**; we then chose diphenyl vinyl carbinol **10** as the source of a stable carbocation.[9] Initially, the dienyl silyl ether **9a** was used as the nucleophilic component, but it was rapidly cleaved back to the conjugated enone **7** under the reaction conditions, giving only traces of alkylation products. The more stable triphenylsilyl ether **9b** gave modest amounts of C-9 alkylation, with a preponderence of C-14 alkylation (α:γ = 3:1). To ensure the stability of the diene component under the reaction conditions and to

simultaneously minimize α-alkylation, we turned to the slightly electron poor dienyls esters **9c-e** and were increasingly rewarded with success. While the dienyl acetate **9c** showed slight improvement over the silyl ether **9b**, the dienyl pivalate **9d** gave ~1:1 α- and γ–alkylations in a combined 90% yield. Best of all, the dienyl triphenylacetate **9e** provided 60-65% yields of the γ-alkylation product **11** along with 25-30% of the α-alkylation product **12**. Other diaryl vinyl carbinols did not offer any significant advantage over **10**. Having screened a wide variety of Lewis acids to generate the diphenyl allyl cation, we found *$ZnBr_2$ to be optimal with CH_2Cl_2-CH_3NO_2 (3:1) as the solvent system of choice.*

Scheme 3: Intramolecular Aldol Reactions



With multiple-gram quantities of the γ-alkylated enone **11** available, the stage was set to explore the key bond construction to C-12. Ozonolysis of the side chain in enone **11** readily formed the enone aldehyde **13** which we hoped to cyclize to the desmethyl scopadulcic acid skeleton by an aldol reaction. While the compound **13** was decomposed by kinetic bases such as LHMDS and LDA, in the presence of bases such as NaOMe, KOtBu and DBU, it showed a great propensity to form the extended enolate into ring-B resulting in the *exclusive formation of the undesired aldol product **14*** in >85% yields.[10] The same product was obtained with p-TSA. Attempted equilibration to the desired **15** was unrewarding.

Treatment of the enone **11** with LDA / THF at -78°C and excess CH_3I gave the C-12 methylated compound **16** (5:2 mixture) which was subjected to ozonolysis and Me_2S work-up to obtain the C-12 methylated enone aldehyde **17** in 65% yield for the two steps. Interestingly, the reaction of **17** with DBU again furnished the C-7 aldol products **18** (1:1 at C-12, separable) by the major pathway along with a trace of the desired aldol product **19** (~7:1 at C-15) resulting from enolization at C-12.

The formation of **19** but not **15** was a subtle clue as to *the importance of the C-12 subtituent in intramolecular bond formation* in abietane skeleta and along with other changes in synthetic design enabled us to achieve our goal as described in the following paper.

Acknowledgement : We thank Prof. A. T. McPhail (Duke University) for X-ray crystallographic determination of the structure of **14** and Dr. A. K Ganguly (SPRI) for his encouragement.

References and Notes

1. Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Shimizu, M.; Suzuki, S.; Yoshizaki, M.; Morita, N.; Tezuka, Y.; Kikuchi, T.; Berganza, L. H.; Ferro, E.; Basualdo, I. *Tetrahedron Lett.* **1987**, *28*, 3693.

2. a) Hayashi, K.; Niwayama, S.; Hayashi, T.; Nago, R.; Ochiai, H.; Morita, N. *Antiviral Research* **1988**, *9*, 345. b) Miyahara, T.; Hayashi, T.; Matsuda, S.; Yamada, R.; Ikeda, K.; Tonoyama, H.; Komiyama, H.; Matsumoto, M.; Nemoto, N.; Sankawa, U. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1037.

3. a) Overman, L. E.; Ricca, D. J.; Tran, V. D. *J. Am. Chem. Soc.* **1993**, *115*, 2042.

b) Ziegler, F. E.; Wallace, O. B. *J. Org. Chem.* **1995**, *60*, 3626.

c) Robichaud, A.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2607.

d) Fox, M. E.; Li, C.; O'Conner, S. J.; Overman, L. E. Abstracts of Papers, 210th National Meeting of the American Chemical Society, Chicago, Il, August 20-24, **1995**. ORGN 285.

4. Tagat, J. R.; Nazareno, D. V.; Puar, M. S.; McCombie, S. W.; Ganguly, A. K. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1101.

5. Abad, A.; Arno, M.; Domingo, L. R.; Zaragosa, R. J. *Tetrahedron* **1985**,*41*, 4937

6. Kirk, D. N.; Wiles, J. M. *J. C. S. Chem. Commun.* **1970**, 1015.

7. Tagat, J. R.; McCombie, S. W.; Ganguly, A. K.; Puar, M. S. *Abstracts of Papers*, 204th National Meeting of the American Chemical Society, Washington, DC, August 23-28, **1992**. ORGN 307.

8. Fleming, I.; Goldhill, J.; Paterson, I. *Tetrahedron Lett.* **1979**, 3209.

9. Kraus, G. A.; Thomas, P. J.; Bougie, D.; Chen, L. *J. Org. Chem.* **1990**, *55*, 1624 : The corresponding 3,3-diphenyl-2-propenyl halides were not as effective as the carbinol **10**.

10. All compounds reported herein were fully characterised by spectral and analytical data. Selected Data:

9d: White crystalline solid. mp: 121-122°C. NMR : δ 1.05 (s, 3H), 1.20 (s, 3H), 1.25 (s, 9H), 1.34 (t, J=4 Hz, 1H), 1.55-1.9 (m, 7H), 2-2.4 (m, 7H), 3.67 (s,3H) and 5.36 (s,1H). $[\alpha]_D^{25}$ = +64.5° (c = 1; $CHCl_3$).

11: White foamy solid. mp: 67-69°C. NMR (300 MHz;$CDCl_3$): δ 0.97 (s,3H), 1.22 (s, 3H), 1.3-1.34 (m, 3H), 1.45-1.72 (m, 6H), 2.1 (m, 1H), 2.27-2.49 (m, 3H), 2.5-2.65(m,3H), 2.92 (dd, J = 5.2, 15Hz, 1H), 3.65 (s, 3H), 5.96(dd, J = 5.2, 9.5 Hz, 1H), 6.07 (s, 1H), 7-7.1 (dd, J = 2, 7 Hz, 2H), 7.25 (m, 4H) and 7.4 (m, 4H). MS(CI): 483(MH^+). $C_{33}H_{38}O_3$ requires C = 82.12; H = 7.94. Found: C = 82.32; H = 8.18. $[\alpha]_D^{25}$ = +167° (c = 2.5; $CHCl_3$).

14: White solid. mp: 168-170°C. NMR(300 MHz; $CDCl_3$): δ 0.89 (s, 3H), 1.17 (s, 3H), 1.31-1.45 (m, 4H), 1.59-1.78 (m, 5H), 1.9 (br-s, OH), 1.97 (dd, J=4,13 Hz, 1H), 2-2.15 (m,2H), 2.36 (m,2H), 2.54 (t, J=3Hz, 1H), 2.73 (dd, J=7,14 Hz, 1H), 3.68 (s, 3H), 4.12 (dd, J=2.2, 7.2 Hz, 1H) and 6.02 (s, 1H). MS (CI): 333 (MH^+). $[\alpha]_D^{23}$ = - 45.5° (c = 0.25; $CHCl_3$).

19: Colorless film. NMR (300 MHz; $CDCl_3$): δ 0.74 (s, 3H-minor), 0.92 (s, 3H-major), 1.0 (m,1H), 1.1(s,3H-major), 1.14 (s,3H-minor), 1.2 (s,3H-major), 1.23 (s,3H-minor), 1.25-1.35 (m, 3H), 1.4-1.75 (m,6H), 1.8 (d, J = 11.6Hz, 1H), 1.95 (dd, J=4,13 Hz, 1H), 2.07 (dd, J=2.8,12.8 Hz, 1H), 2.17 (dd, J=2,7 Hz,1H), 2.22 (dd, J =2,7 Hz, 1H), 2.48 (m, 2H), 3.62 (s, 3H-major), 3.65 (s, 3H-minor), 3.85 (t, J=2.5Hz,1H-major), 4.2 (m, 1H-minor), 5.6 (s, 1H-major) and 5.8 (s, 1H-minor).

(*Received in USA* 19 *August* 1996; *accepted* 30 *September* 1996)