Pergamon

Tetrahedron Letters, Vol. 37, No. 47, pp. 8463-8466, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01948-X

A Scalemic Synthesis of the Scopadulcic Acid Skeleton. II: Ring-D Formation via Regiospecific Intramolecular Aldol and Alkylation Reactions

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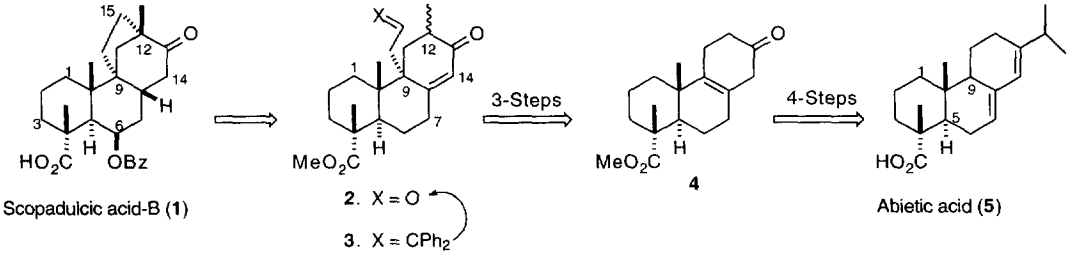
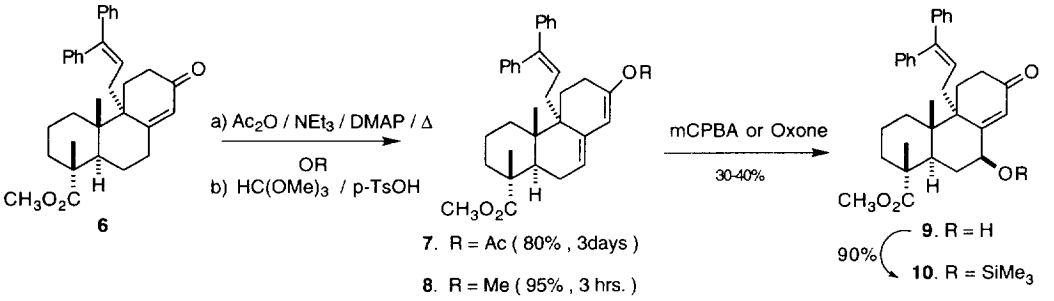
Abstract : The propensity of abietenones such as **2** to form exclusively the extended enol(ate) into ring-B can be curbed by introducing an alkoxy group at C-7 in the abietane framework. Thus, the 7- trimethylsilyloxy enone-aldehydes **11** and **13** cyclize to form only the C-12 aldol products **12** and **14**. Furthermore, the 9-iodoethyl-12-methyl-enone **19** cyclizes via its putative enol to give only the tetracyclic enone **20**. Compounds **12** and **20** contain the complete carbon skeleton of scopadulcic acid B. Copyright © 1996 Elsevier Science Ltd

In the preceding paper[1], we described an approach to scopadulcic acid-B (SA-B, **1**) via an intramolecular aldol reaction of precursor **2** which was obtained by ozonolysis of the C-9 sidechain in **3**. The latter was prepared by an efficient 7-step sequence from commercially available abietic acid employing a novel *intermolecular γ-alkylation of skipped enone* **4** as the key step. This approach suffered from the unexpected tendency of systems such as **2** to prefer bond formation at C-7 nearly exclusively. This conjugated dienol(ate) formation is a consequence of the $\Delta^{8,14}$-double bond which is required to facilitate the functionalization of ring-B at a later stage. In lieu of deleting this double bond, we considered the possibility of functionalizing ring-B in a manner that would deactivate C-7 towards aldol reaction. Alternatively, if the C-7 aldol product reflects a thermodynamic sink, we wondered if an *intramolecular alkylation via a kinetically controlled enolization* would give the desired product of C-9 → C-12 bond formation. Herein, we report the successful application of both of these strategies to complete the scopadulan system.



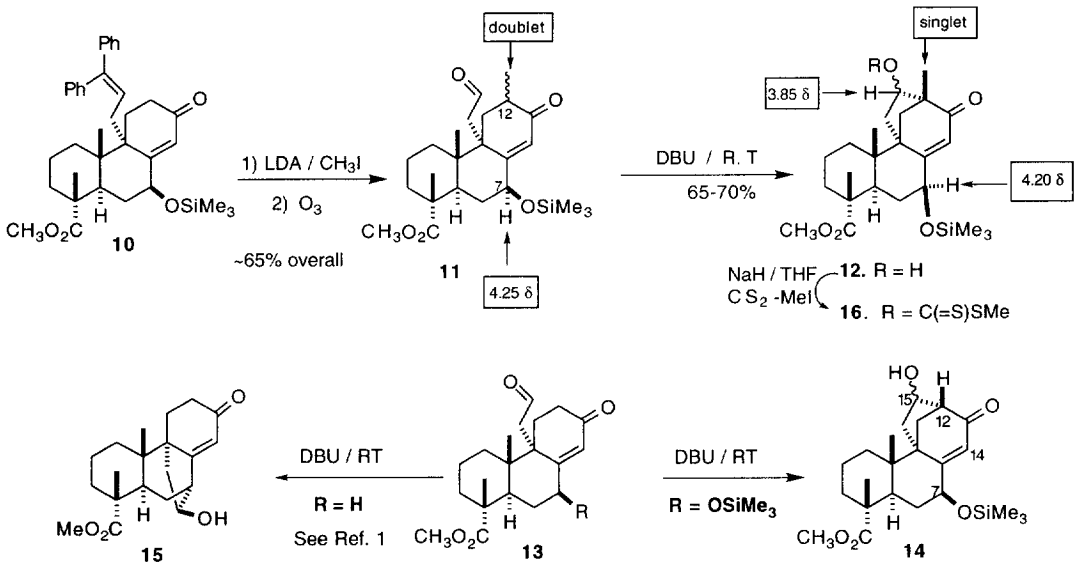
We decided to exploit the well-known tendency of α-alkoxy ketones to enolize away from the oxygen substituent.[2] Accordingly, the γ-alkylated enone **6**[1] was converted to the dienol derivatives[3] **7** or **8**; oxidation with m-CPBA or oxone gave the 7-hydroxy enones **9** (~12:1 mixture of β/α; only the major 7β-isomer is shown) in modest yields.[4] Silylation of **9** (TMSOTf / Pyridine) produced **10** .

Scheme 1: Synthesis of the 7-OTMS Derivative



Methylation of **10** at C-12 was carried out under kinetic conditions followed by ozonolytic cleavage of the C-9 sidechain to expose the enone-aldehyde **11** in high overall yield. Upon exposure to DBU at room temperature, we were gratified to find that ***11*** *enolizes* ***exclusively*** *at C-12 to give the desired aldol product* ***12*** *(~20:1 mixture at C-15) incorporating the scopadulcic acid-B skeleton.*[5] The 12-CH_3 and the 7-OTMS substituents serve as useful markers in the proton NMR spectrum: The diastereomeric mixture of doublets typical of the 12-CH_3 signals in **11** collapse to a sharp singlet in the product **12**; the 7-H signal at δ 4.2 is intact in the product and a new methine at δ 3.85 signals the newly formed 2° alcohol. The directing effect of the OTMS substituent is further demonstrated by the cyclization of the 12-desmethyl-7-trimethylsilyloxy enone aldehyde **13** to the desmethyl scopadulan system **14** (~5:1 mixture at C-15).[6]

Scheme 2: Aldol Reactions of the 7-OTMS Enone-Aldehydes



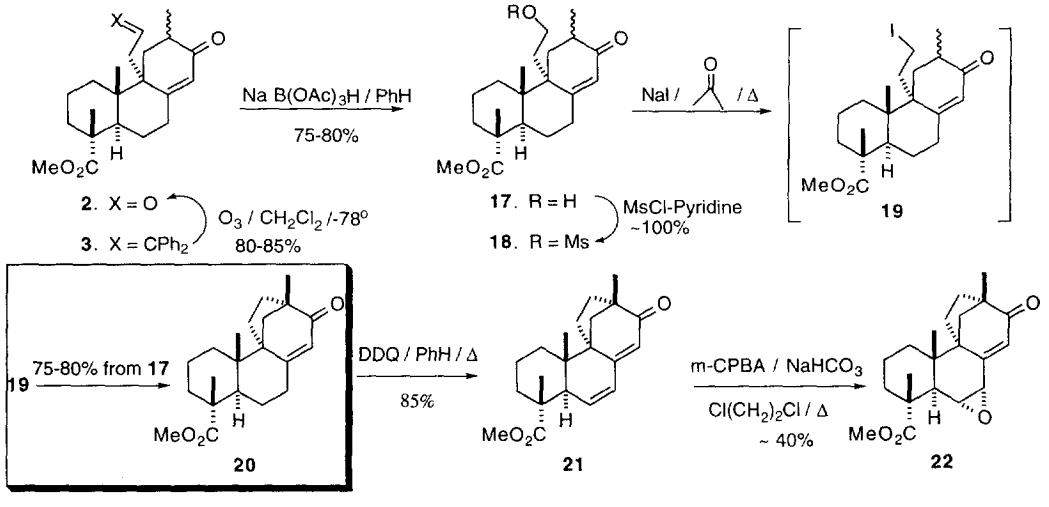
The next task at hand was selective deoxygenation of the 2° alcohol in the newly formed D-ring in the advanced intermediate **12**. This turned out to be unexpectedly non-trivial: the neopentyl alcohol failed to react

with thiocarbonyl diimidazole and other thionoylating reagents. However, exposure to NaH in THF followed by sequential treatment with CS_2 and MeI furnished the xanthate ester **16** in 80% yield. Unfortunately, the reaction of the xanthate with Bu_3SnH-AIBN in refluxing benzene gave a multi-component mixture. All attempts to improve this deoxygenation were to no avail.

Finally, we decided to revisit the *intramolecular alkylation* strategy. Early efforts in this regard using the des-12-methyl enone bearing an iodoethyl sidechain at C-9 led only to alkylation at C-14. Would the 12-methyl compound i.e. **19** with or without the 7-OTMS group behave differently ?

Accordingly, our key-intermediate **6** was methylated (LDA/THF/MeI) to give **3** and then ozonized to obtain the 12-methyl enone aldehyde **2**. Selective reduction of the sidechain was achieved with $Na(OAc)_3BH$ and the alcohol was converted to the mesylate **18**, all in very good overall yield. Attempted alkylation with the mesylate using NaOMe, KOtBu, DBU etc resulted in cleavage of **18** back to alcohol **17**. Direct conversion of the alcohol to iodide was low yielding. When a solution of the mesylate **18** and excess (3eq.) NaI in acetone was refluxed, clean conversion to the 9-iodoethyl-12-methyl-enone **19** was observed initially (3-4h); this was followed by slower, but eventually (~7h) *complete conversion* to a new product which turned out to be the desired tetracyclic enone **20**.

Scheme 3: Intramolecular Alkylation of the 9-Iodoethyl-12-Methyl Enone



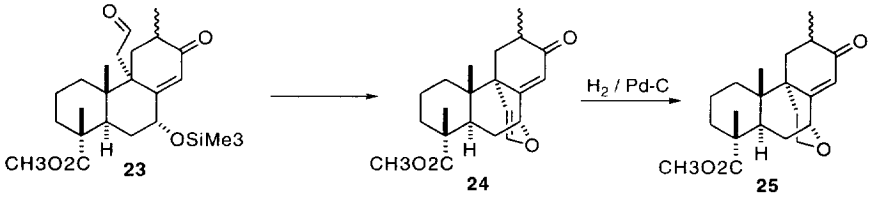
Prior to discovering the NaI mediated cyclization, the 9-iodoethyl enone **19** prepared directly from alcohol **17** was subjected to a variety of base mediated conditions (KHMDS, LDA, NaOMe, KOtBu etc) leading only to trace amounts of **20** and *recovered* **19**. Additionally, the presence of $NaHCO_3$ during the Finkelstein exchange step retarded the formation of **20** indicating that perhaps adventitious acid catalyzes the formation of 12-13 enol intermediate which, promoted by proximity, undergoes an unusual cyclization on to a relatively weak electrophile, providing the target skeleton. Classical DDQ oxidation of **20** proceeded smoothly to the tetracyclic dienone **21** in high yield. Under non-neutral conditions, the dienone **21** seems to enolize via loss of the 5-H to form a tri-enol that reacts in the C-ring ; buffering with $NaHCO_3$ was essential during the oxidation of the $\Delta^{6,7}$-double bond with m-CPBA in refluxing dichloroethane. The last reaction gave only the α-epoxide albeit in modest yield.

In summary, we have described a short (abietic acid to **20** in 10 steps, ~11% overall yield), scalemic synthesis of the entire carbon framework of the scopadulcic acids, with functional handles to explore structure-activity relationship in every ring. The tricyclic enones used in this study may find applications in the synthesis of other terpenoids. The γ-alkylation of an enone reported in the preceding paper and the use of TMSO-group to control regiochemistry of enolizations discussed in this paper should find general utility.

Acknowledgement : We thank Dr. A. K. Ganguly (SPRI) for his support and encouragement.

References and Notes

1. Tagat, J. R.; McCombie, S. W.; Puar, M. S. *Tetrahedron Lett.* preceding paper in this issue.
2 a). Hirsch, J. A.; Wang, X. L. *Synth. Comm.* **1982**, *12*, 333.
b). Goldsmith, D. J.; Dickinson, C. M.; Lewis, A. J. *Heterocycles* **1987**, *25*, 291.
3. The C-9 *unsubstituted* abietenone forms dienol derivatives rapidly (1-4h) and their oxidation is also a quick reaction proceeding stereoselectively to 7α-hydroxy enone in high yield (see ref.1).
4. a). Suryavanshi, S. N.; Fuchs, P. L. *Tetrahedron Lett.* **1981**, *22*, 4201.
b). Suryavanshi, S. N.; Fuchs, P. L. *J. Org. Chem.* **1986**, *51*, 902.
5. The 7α-trimethylsilyloxy enone aldehyde **23** spontaneously cyclizes to **24** which was reduced to **25**:



6. All compounds described herein were fully characterized by spectral and analytical data. Selected Data:
12: White foam. NMR (300MHz;$CDCl_3$): δ 0.02 (s,9H), 0.88 (s, 3H), 1.09 (s, 3H), 1.18 (s, 3H), 1.25 (dd, J=2.6,11.4 Hz, 1H), 1.5-1.58 (m, 5H), 1.6-1.8 (m, 5H), 1.91 (dd, J=4.9,12.7 Hz, 1H), 2.53 (dd, J=2.8, 12.7 Hz, 1H), 2.72 (dd, J=2,7.2 Hz, 1H), 3.61 (s, 3H), 3.85 (dd, J=5,7 Hz, 1H), 4.32 (dd, J=2.8, 6 Hz, 1H) and 5.68 (s, 1H). $C_{24}H_{39}O_5Si$ (MH^+) requires 435.2567. Found: 435.2557.
14: White solid. NMR (300 MHz; $CDCl_3$): δ 0.02 (s, 9H-major), 0.04 (s, 9H-minor), 0.88 (s, 3H-minor), 0.93 (s, 3H-major), 1.21 (s, 3H-major), 1.22 (s, 3H-minor), 1.3 (t, J=2.5 Hz, 1H), 1.55-1.7 (m, 5H), 1.7-1.95 (m, 5H), 2.0 (br-s,1H), 2.05 (dd, J=5,13 Hz, 1H), 2.52 (dd, J=3.8,12.5 Hz, 1H), 2.70 (m, 1H), 3.63 (s, 3H), 4.2 (dd, J=5,7 Hz, 1H), 4.34 (t, J=2.5 Hz, 1H), 5.63 (s, 1H-major) and 6.02 (s, 1H-minor). MS(CI): 421 (MH^+).
20: White solid. mp:134-136°C. $[\alpha]_D^{25}$ = +95.5° (c = 0.11; $CHCl_3$). NMR(300 MHz; $CDCl_3$): δ 0.99 (s, 3H), 1.19 (s, 3H), 1.26 (s, 3H), 1.3 (m, 2H), 1.5-1.75 (m, 11H), 2.17 (dd, J=3,13 Hz, 1H), 2.2-2.3 (m, 1H), 2.54 (m, 2H), 3.67 (s, 3H) and 5,74 (s, 1H). $C_{21}H_{31}O_3$ (MH^+) requires 331.2273; Found: 331.2284.
21: Off-white solid. mp: 100-101°C. $[\alpha]_D^{25}$ = -38.2° (c = 0.15; $CHCl_3$). NMR(300 MHz; $CDCl_3$): δ 0.99 (s, 3H), 1.23 (s, 3H), 1.30 (s, 3H), 1.45-1.8(m, 11H), 2.25 (m, 1H), 2.85 (t, J=2 Hz, 1H), 3.7(s, 3H), 5.7 (s, 1H), 5.9 (dd, J=2.8, 9.7 Hz, 1H) and 6.21 (dd, J=2.8, 9.7 Hz, 1H). $C_{21}H_{29}O_3$ (MH^+) requires 329.2117; Found: 329.2110.

(*Received in USA* 19 *August* 1996; *accepted* 25 *September* 1996)