Pergamon

Tetrahedron Letters 42 (2001) 7855–7857

TETRAHEDRON LETTERS

# Stereo- and regio-selective Ti-mediated radical cyclization of epoxy-alkenes: synthesis of the A and C ring synthons of paclitaxel

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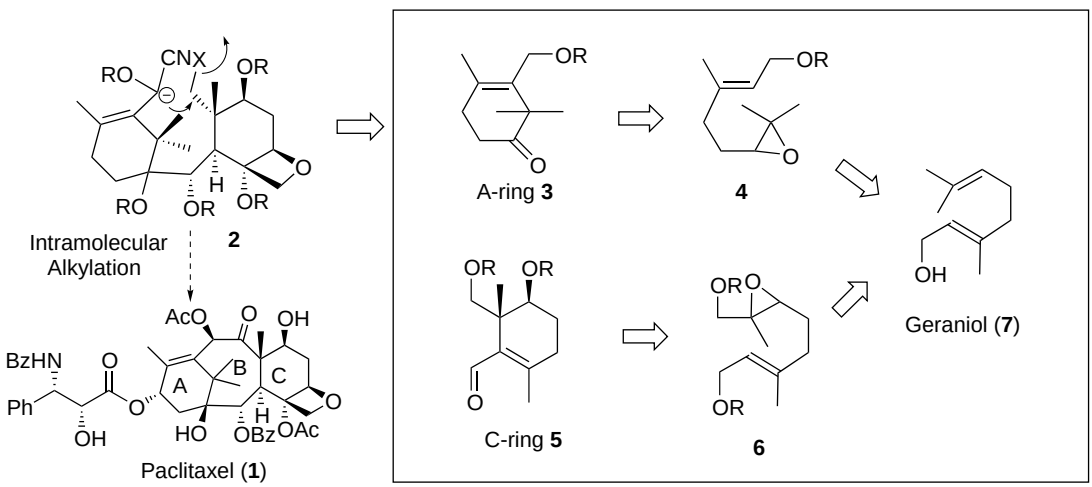
Received 16 July 2001; revised 20 August 2001; accepted 31 August 2001

**Abstract**—We have developed a practical synthetic route for the A and C rings of paclitaxel. The key reaction is a Ti-mediated radical cyclization of an epoxyalkene. 

Paclitaxel (**1**) is a potent antitumor agent that consists of fully functionalized ABCD ring system including a highly strained 8-membered B ring.[1] Our synthetic strategy is to close the B ring at a late stage of the synthesis by intramolecular cyanohydrin alkylation of **2** as we previously reported in the model ABC ring system (Scheme 1).[2] We wish to report[3] a Ti-mediated radical cyclization of epoxyalkenes **4** and **6** to synthesize an A ring moiety **3** and a C ring synthon **5**, both of which were prepared from geraniol (**7**).[4]

We first describe the synthesis of the A ring moiety **3** (Scheme 2). Epoxyalkene **4** (R = Ac) readily prepared from geraniol was treated with 2.5 equiv. of $Cp_2TiCl$[5] (prepared in situ from $Cp_2TiCl_2$ and Zn-dust in THF) at room temperature. Ring opening of the epoxide, followed by concomitant radical cyclization provided *exo*- and *endo*-olefin mixture **8** in 72% combined yield.[6] Interestingly, termination of this radical cyclization is not reductive as reported by RajanBabu,[5] rather it involves β-hydrogen elimination, providing an alkene




**Scheme 1.** Synthetic strategy for the A and C rings of paclitaxel from geraniol.

*Keywords*: cyclisation; epoxides; stereocontrol; taxoids; titanium and compounds.

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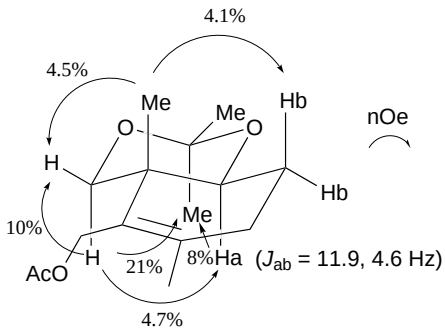
0040-4039/01/$ - see front matter 
PII: S0040-4039(01)01655-0

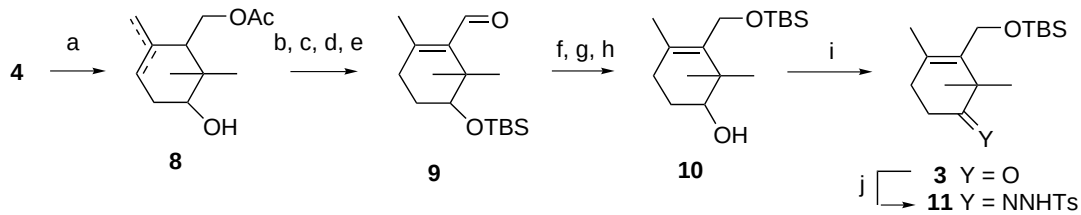
function. This observation is consistent with the recent report of Barrero et al.[7] Protection of the secondary alcohol with TBS, hydrolysis of the acetoxy group, and Swern oxidation of the resulting alcohol afforded an aldehyde whose double bond isomerized to the α,β-unsaturated **9** upon DBU treatment.[8] Reduction of enal **9**, deprotection of the TBS, followed by selective protection of the primary alcohol provided alcohol **10**. Swern oxidation of **10** gave desired ketone **3**, which was converted to tosylhydrazone **11** according to the reported procedure.[9]

We next investigated the stereochemistry of the Ti-mediated radical cyclization of **6** (Scheme 1). The allylic alcohol **12**[10] and its protected derivatives **13a–d** were subjected to this reaction (Scheme 3). The results are depicted in Table 1. The protection of the epoxy alcohol is necessary to achieve the cyclization, as the free alcohol **12** exclusively gave reduced product **17**.[11] How ever, the reactions of **13a–d** afforded the desired cyclized products **14a–d** as mixtures of diastereomers of *endo*- and *exo*-olefins. We subjected these mixtures to an additional four steps, to investigate the stereoselection at the cyclization stage. Protection of the secondary alcohol of **14** with TBS and hydrolysis of the acetate afforded the alcohol. The primary alcohol was oxidized to the aldehyde and the mixture of alkene moieties isomerized to the α,β-unsaturated aldehyde upon DBU treatment. The products obtained, **15** and **16**, are diastereomers at the C7 and C8 positions.[8] The diastereomer ratio increased with the ethereal protection of the epoxy alcohol and a benzyloxymethyl group afforded the best results (**15a**:**16a** = 4.5:1) when the reaction was carried out at 0 °C (Entry 3).[12] Presumably, a 6-membered chelation **A** is important to produce the desired stereochemistry at the C8 position. The stereochemistry of **15** was established from nOe determinations on the bicyclic compound **18**.[13]

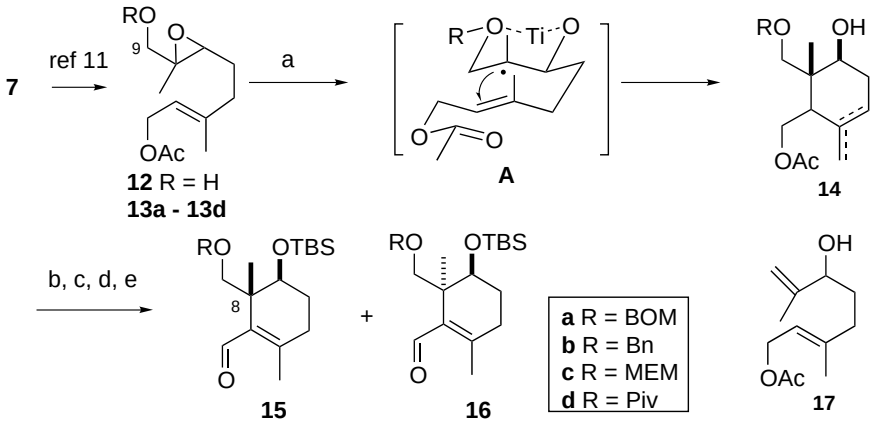



**18**

We have demonstrated that the Ti-mediated radical cyclization of epoxy alkenes prepared from geraniol provides the important synthetic intermediates for both A ring and C ring synthons for the synthesis of paclitaxel. Further synthetic study is presented in the following paper.




**Scheme 2.** The synthesis of A ring **3** by way of Ti-mediated cyclization (a) 2.5 equiv. $Cp_2TiCl_2$, Zn, THF, 78%; (b) TBSOTf, 2,6-Lutidine, $CH_2Cl_2$; (c) $K_2CO_3$, MeOH; (d) Swern Oxid.; (e) DBU, $CH_2Cl_2$ 60% (4 steps); (f) $NaBH_4$, MeOH; (g) TBAF, THF; (h) TBSCl, $NEt_3$, $CH_2Cl_2$; (i) Swern Oxid. 71% (4 steps); (j) $NH_2NHTs$, THF.




**Scheme 3.** (a) $Cp_2TiCl_2$, Zn, THF (see Table 1); (b) TBSOTf, 2,6-lutidine, $CH_2Cl_2$; (c) $LiAlH_4$, ether; (d) $SO_3$·Py, $NEt_3$, DMSO; (e) DBU, $CH_2Cl_2$, 38% (4 steps).

**Table 1.** Stereoselectivity of radical cyclization of **12** and **13a–d**

| Entry | Substrate | Temperature (°C) | Yield[a] (%) | Ratio[b] (**15**:**16**) |
|---|---|---|---|---|
| 1 | **12** | 20 | (27[c]) | – |
| 2 | **13a** | 20 | 85 | 2.7: 1 |
| 3 | **13a** | 0 | 80 | 4.5: 1 |
| 4 | **13b** | 20 | 79 | 2.5: 1 |
| 5 | **13c** | 20 | 51(13[c]) | 2.7: 1 |
| 6 | **13d** | 20 | 89 | 1.8: 1 |

[a] Yields in cyclization reaction.
[b] This ratio was determined by $^1$H NMR (270 MHz).
[c] The formation of **17** was found at the cyclization stage.

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6. *exo*-Olefin 46% (77:23 diastereomer mixture), *endo*-olefin (26%, 60:40 diastereomer mixture), and non-olefin (6%) were isolated. Five-*exo* cyclization was also observed by the formation of 2,2,3-trimethyl-3-vinylcyclopentan-1-ol (12%, 51:49 diastereomer mixture).
7. A report performed on various geraniol derivatives appeared during the preparation of this manuscript, see: Barrero, A. F.; Cuerva, J. M.; Herrador, M. M.; Valdivia, M. V. *J. Org. Chem.* **2001**, *66*, 4074–4078.
8. All new compounds reported here were characterized on the basis of their spectral data ($^1$H and $^{13}$C NMR, IR). Selected spectral data for compound **9**: $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 0.06 (s, 6H), 0.89 (s, 9H), 1.16 (s, 3H), 1.19 (s, 3H), 1.64–1.80 (m, 2H), 2.08 (s, 3H), 2.08–2.42 (m, 2H), 3.44 (dd, 1H, $J=7.6$, 3.4 Hz), 10.09 (s, 1H); $^{13}$C NMR (67.8 MHz, $CDCl_3$), $\delta$ −4.8, −4.1, 18.2, 19.2, 21.8, 26.0, 26.4, 32.7, 38.5, 76.3, 139.3, 154.5, 192.6; IR (neat) 2948, 1673, 1460, 1380, 1253, 1085, 885, 837, 774 cm$^{-1}$; **15a**: $^1$H NMR (270 MHz, $CDCl_3$), $\delta$ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.08 (s, 3H), 1.61–1.81 (m, 2H), 2.10 (s, 3H), 2.26–2.44 (m, 2H), 3.57 (d, 1H, $J=8.9$ Hz), 3.95 (dd, 1H, $J=6.6$, 7.9 Hz), 4.13 (d, 1H, $J=8.9$ Hz), 4.45 (d, 1H, $J=11.9$ Hz), 4.55 (d, 1H, $J=11.9$ Hz), 4.64 (d, 1H, $J=6.6$ Hz), 4.68 (d, 1H, $J=6.6$ Hz), 7.20–7.44 (m, 5H), 10.12 (s, 1H); $^{13}$C NMR (67.8 MHz, $CDCl_3$), $\delta$ −4.9(q), −3.8(q), 16.9(q), 18.1(s), 19.2(q), 25.9(q), 26.4(t), 33.6(t), 43.1(s), 69.4(t), 69.88(t), 69.95(d), 95.1(t), 127.6(d), 127.9(d), 128.4(d), 136.6(s), 138.0(s), 156.2(s), 192.1(d); IR (neat) 2946, 1675, 1459, 1381, 1253, 1113, 1047, 837, 777, 699 cm$^{-1}$; **16a**: $^1$H NMR (270 MHz, $CDCl_3$), $\delta$ 0.06 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.21 (s, 3H), 1.62–1.81 (m, 2H), 2.13 (s, 3H), 2.20–2.44 (m, 2H), 3.63 (dd, 1H, $J=3.3$, 9.9 Hz), 3.70 (d, 1H, $J=8.9$ Hz), 4.04 (d, 1H, $J=8.9$ Hz), 4.50 (d, 1H, $J=11.9$ Hz), 4.57 (d, 1H, $J=11.9$ Hz), 4.63 (d, 1H, $J=6.3$ Hz), 4.69 (d, 1H, $J=6.3$ Hz), 7.25–7.40 (m, 5H), 10.10 (s, 1H); $^{13}$C NMR (67.8 MHz, $CDCl_3$), $\delta$ −4.9(q), −3.9(q), 18.2(s), 19.7(q), 22.0(q), 26.0(q), 26.9(t), 33.3(t), 42.5(s), 69.1(t), 69.9(t), 74.6(d), 94.8(t), 128.0(d), 128.4(d), 128.5(d), 136.0(s), 138.2(s), 156.4(s), 192.6(d); IR (neat) 2948, 1677, 1468, 1381, 1253, 1106, 1050, 836, 777, 698 cm$^{-1}$.
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12. Five-*exo* cyclization was also observed by the formation of 2-(benzyloxymethyloxy)-2,3-dimethyl-3-vinylcyclopentan-1-ol (14%).
13. Preparation of **18** from **15a** (i) $NaBH_4$, MeOH; (ii) TBAF, THF; (iii) TBSCl, $NEt_3$, $CH_2Cl_2$; (iv) Na, $NH_3$; (v) 2,2-dimethoxypropane, CSA, $CH_2Cl_2$; (vi) TBAF, THF; (vii) $Ac_2O$, DMAP, $CH_2Cl_2$.