Pergamon

Tetrahedron Letters 43 (2002) 3573–3576

TETRAHEDRON LETTERS

The synthesis of *epi*-epoxydon utilising the Baylis–Hillman reaction

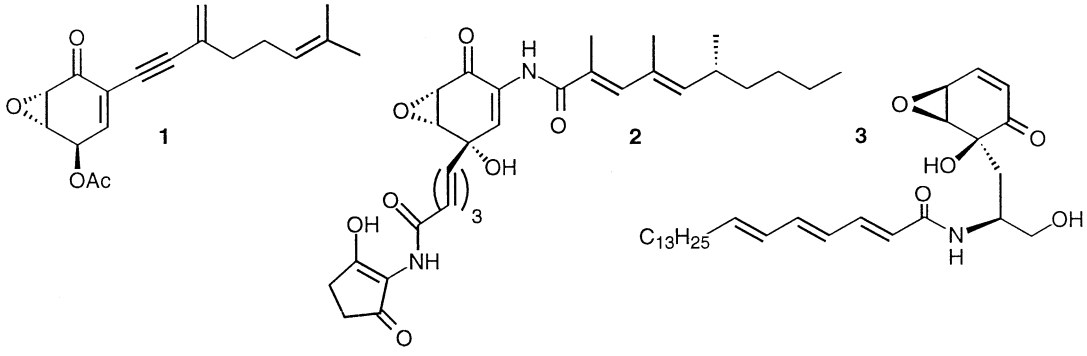
Thorsten Genski and Richard J. K. Taylor*

Department of Chemistry, University of York, Heslington, York YO10 5DD, UK

Received 18 February 2002; revised 8 March 2002; accepted 15 March 2002

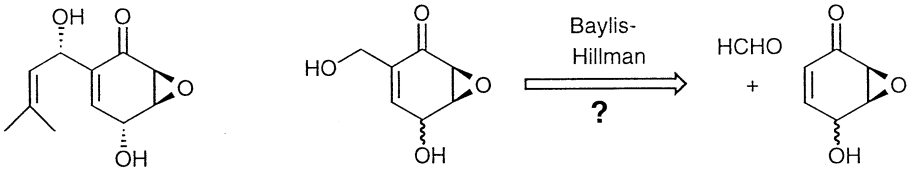
Abstract—(±)-*epi*-Epoxydon was synthesised by means of a triethylaluminium/tri-*n*-butylphosphine-catalysed Baylis–Hillman reaction between an *O*-protected epoxidised hydroxyquinol core and paraformaldehyde, constituting the first application of the Baylis–Hillman reaction to a highly functionalised β-substituted enone.

We have a long-standing interest in synthetic approaches to epoxycyclohexenone-based natural products. Recent examples include tricholomenyn A **1**,[1] manumycin A **2**[2] and scyphostatin **3**.[3]



A number of related epoxycyclohexenone-based natural products are known which contain additional hydroxyalkyl substituents.[4–7] Examples are panepoxydon **4**,[4] epoxydon **5**[5] and *epi*-epoxydon **6**.[6] Panepoxydon is a potent NF-κB inhibitor,[4] and epoxydon and *epi*-epoxydon exhibit antifungal, antibacterial and phytotoxic activity.[5,6] We considered the possibility of preparing such compounds from the corresponding cyclohexenones via the Baylis–Hillman reaction.[8] Thus, for example, epoxydon **5** and *epi*-epoxydon **6** would be prepared from the Baylis–Hillman reaction between formaldehyde and enones **7** and **8**, respectively, as shown in Scheme 1.

The Baylis–Hillman reaction has attracted considerable interest due to its potential for forming a carbon–car-



4 **5**, β-OH **6**, α-OH **7**, β-OH **8**, α-OH

Scheme 1.

* Corresponding author.

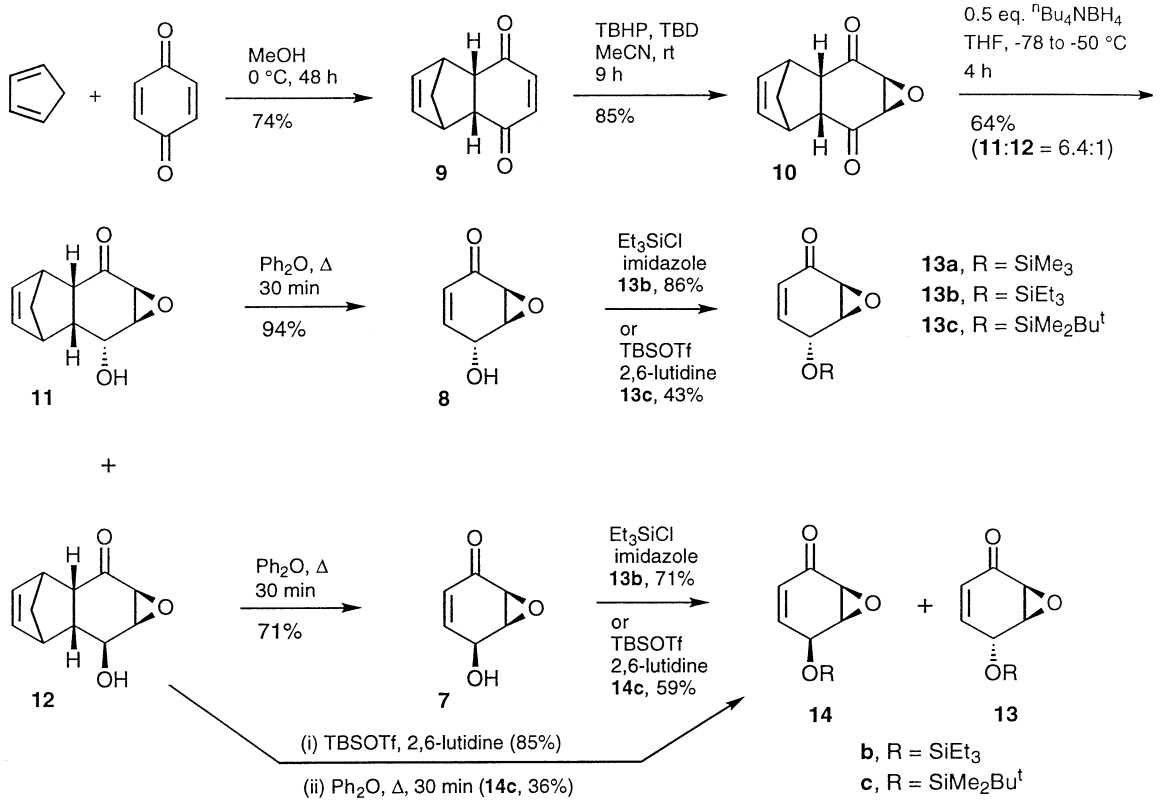
0040-4039/02/$ - see front matter
PII: S0040-4039(02)00529-4

bon bond between the α-position of an activated alkene and an aldehyde/ketone or imine in one step by nucleophilic catalysis using a tertiary amine or phosphine.[8] The reaction proceeds best with sterically unhindered alkenes; β-substituted alkenes usually require increased pressure and often afford mixtures of *E*- and *Z*-isomeric products.[8] Recently it has been demonstrated that the Baylis–Hillman reaction of β-substituted alkenes can be carried out at atmospheric pressure by the use of sulfides,[9a,9b] selenides[9a,9c] and tertiary amines[9d] in the presence of titanium(IV) tetrachloride, as well as DABCO in combination with lithium perchlorate,[9e] DMAP,[9f] DBU[9g] and 3-hydroxyquinuclidine in water/formamide.[9h] In most synthetic applications the Baylis–Hillman reaction has been applied to simple activated alkenes at an early stage of the synthetic route, or if utilised at a more advanced stage, the substrate has contained little if any functionality other than the activated alkene itself.[10] Thus, the successful application of the Baylis–Hillman reaction to the synthesis of epoxydon **5** and *epi*-epoxydon **6**, as shown in Scheme 1, would demonstrate the utility of the procedure with functionalised, β-substituted enones.

A number of routes have been described to prepare the epoxy quinols **7** and **8**, and the silylated analogues **13** and **14**, required for this study.[11,12] We developed a streamlined version of Ogasawara's route[12a] (Scheme 2);[13] after the completion of this part of our study Lubineau and Billault published a closely related route to epoxy quinol **8**.[12b]

Thus, as reported,[14] addition of *p*-benzoquinone to 1,3-cyclopentadiene afforded *endo*-adduct **9** in good yield after recrystallisation. A number of attempts were made to reduce selectively one carbonyl group of **9** but the best yield of the corresponding hydroxy ketone was only 8%. We therefore first carried out the epoxidation of **9**. This was achieved in good yield, and with complete *exo*-stereoselectively, using *tert*-butyl hydroperoxide (TBHP, 2 equiv.) and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, 0.05 equiv.).[15] Reduction of epoxide **10** using L-Selectride® or Super-Hydride® was totally stereoselective giving **11** in 52% yield in both cases. Tetra-*n*-butylammonium borohydride[16] gave a mixture of **11** and **12** (64%; 74% based on recovered starting material; **11**:**12** = 6.4:1), which could be separated by chromatography on silica (Et_2O/petrol ether, 5:1). Retro-Diels–Alder reaction of separated **11** and **12** took place efficiently in refluxing diphenyl ether to give *trans*-epoxy alcohol **8** in 94% yield and the *cis*-epimer **7** in 71% yield.

Silyl protected analogues epoxy quinols **13** and **14** were also prepared (Scheme 2). Attempts to prepare the trimethylsilyl-derivative **13a** of the *trans*-epoxy alcohol **8** were unsuccessful: the trimethylsilyl-derivative of **11** decomposed on thermolysis, and the trimethylsilylation product of epoxyquinol **8** proved to be extremely unstable to purification on silica. Fortunately, the triethylsilyl analogue **13b** could be obtained directly from alcohol **8** in 86% yield after chromatography. The *t*-butyldimethylsilyl (TBS)-derivative **13c** was prepared in a similar way, albeit in lower yield



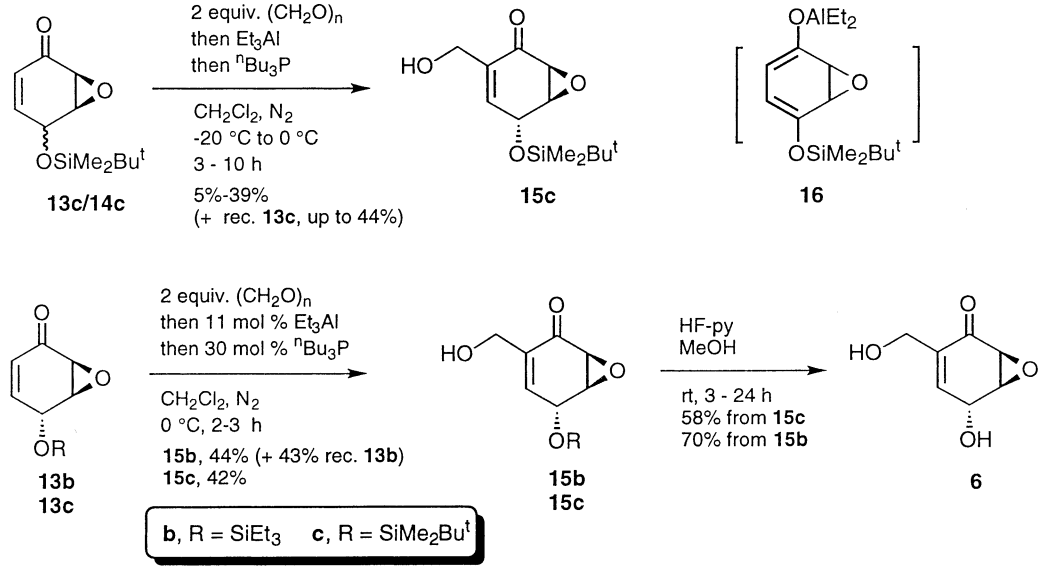
Scheme 2.

(**13c** was also obtained in 76% yield by thermolysis of the silylated analogue of **11**). The direct silylation route was not so straightforward with the *cis*-epoxy alcohol **7**, however. Triethylsilylation of **7** using triethylsilyl chloride/imidazole gave complete epimerisation to produce **13b** in 71% yield. Similar equilibration processes have been reported before.[5] No epimerisation was observed using TBSOTf/2,6-lutidine, however, with **14c** being obtained in 59% yield. The retro-Diels–Alder reaction sequence could also be employed to prepare a sample of **14c** devoid of its epimer.

With the epoxy quinols in hand, we set out to examine the suitability of various Baylis–Hillman protocols for this class of highly functionalised substrate (Scheme 3). We realised that the correct choice of conditions would be crucial as epoxy quinols are known to be prone to aromatisation, and epoxydon and *epi*-epoxydon have been reported to be unstable in the presence of weak bases such as aqueous sodium acetate or pyridine.[5,6] All attempts to convert the unprotected epoxy quinols **7** and **8** directly into racemic epoxydon and *epi*-epoxydon, respectively, using formaldehyde under amine catalysis (DMAP, DABCO, 3-quinuclidinol and Et_3N) gave only decomposition. However, when triethylaluminium in the presence of tri-*n*-butylphosphine[17] was utilised, the formation of a more polar product was observed, although we were unable to isolate it from the reaction mixture. When moving on to study the use of the silylated hydroxy quinols in the Baylis–Hillman reaction, we therefore concentrated our efforts on the $Et_3Al/^nBu_3P$ catalytic system.

In the initial studies a mixture of **13c** and **14c** (ca. 12:1) and paraformaldehyde (2 equiv.) in dichloromethane was treated with 30 mol% of tri-*n*-butylphosphine and 11 mol% of triethylaluminium at temperatures between –20°C and 0°C for 3–10 hours. The Baylis–Hillman product **15c** was observed in all cases (5–39%) along with unreacted starting material. It was noticed (TLC) that decomposition of the substrates and the product occurred when the reaction temperature exceeded 5°C. The longer reaction times also resulted in somewhat lower yields. The order in which the reagents were added turned out to be crucial to the outcome of the process. The epoxyquinols were unstable when exposed to $^nBu_3P$ before addition of triethylaluminium. Thus, paraformaldehyde, Et_3Al and $^nBu_3P$ were added rapidly in that order. Increasing the number of equivalents of both catalysts together (0.4 equiv. Et_3Al, 1 equiv. $^nBu_3P$) led mainly to decomposition of the substrates, while raising the concentration of $^nBu_3P$ alone (2.6 equiv.) did not have any significant effect on the product yield (34%). These results imply that Et_3Al is responsible for the decomposition of the starting material. Decreasing the amount of both catalysts (0.05 equiv. Et_3Al, 0.1 equiv. $^nBu_3P$), resulted in longer times (10 h) and a reduced yield (15%). Comparison of the amount of recovered starting material also indicates its instability towards the catalytic system, since twice as much was regained at lower concentration of the catalysts. It should be noted, however, that the Lewis acid was essential, as the use of $^nBu_3P$ alone caused enone decomposition (and triphenylphosphine alone gave no reaction).

The only product isolated from this study was the *trans*-epoxy ketone adduct **15c**, and when unreacted starting material was recovered, the only isomer observed was the *trans*-epoxy ketone **13c**. It could be that selective decomposition of **14c** (or of the *cis*-isomer of adduct **15c**) was occurring. Alternatively, the *cis*-isomer of adduct **15c** could undergo epimerisation. The most likely explanation, given the facile epimerisation observed during the base-mediated silylation of **7** (Scheme 2), is that under these Baylis–Hillman conditions **14c** is epimerised to **13c** by way of an intermediate such as **16**. When more material is available the Baylis–Hillman reaction of pure **14c** will be studied in order to clarify this point.



Scheme 3.

With optimised conditions established, the conversion of **13b** and **13c** into *epi*-epoxydon **6** was carried out (Scheme 3). Thus, **13c** gave **15c** in 42% isolated yield, and **13b** gave **15b** in 44% yield (with 43% of recovered **13b**). Desilylation was effected using pyridine–HF complex; removal of the TBS group was rather slow and low yielding but fortunately the triethylsilyl group was removed in 3 hours and in 70% yield. The structure of the racemic *epi*-epoxydon **6** thus produced was confirmed by comparing its ^{1}H NMR spectroscopic data and melting point (76°C; lit.[18] 78.5–79°C) with the literature.[18]

In conclusion, we have carried out what we believe to be the first application of the Baylis–Hillman reaction to a highly functionalised molecule (containing epoxide and protected alcohol moieties in addition to the β-substituted enone) and utilised the adduct to prepare the bioactive natural product, (±)-*epi*-epoxydon. We are currently optimising this methodology and applying it to the synthesis of more complex natural products.

Acknowledgements

We are grateful to the Deutscher Akademischer Austauschdienst (DAAD) and Elsevier Science for studentship support (T.G.). We also thank Dr. Peter O'Brien (University of York) for helpful discussions.

References

1. Graham, A. E.; Taylor, R. J. K. *J. Chem. Soc., Perkin Trans.* **1997**, *1*, 1087.
2. Alcaraz, L.; Macdonald, G.; Ragot, J. P.; Lewis, N.; Taylor, R. J. K. *J. Org. Chem.* **1998**, *63*, 3526.
3. Runcie, K. A.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 3237.
4. Shotwell, J. B.; Hu, S.; Medina, E.; Abe, M.; Cole, R.; Crews, C. M.; Wood, J. L. *Tetrahedron Lett.* **2000**, *41*, 9639 and references therein.
5. (a) Sakai, R.; Sata, R.; Niki, H.; Sakamura, S. *Plant Cell Physiol.* **1970**, *11*, 907; (b) Ichihara, A.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1972**, *13*, 5105; (c) Ichihara, A.; Oda, K.; Sakamura, S. *Agric. Biol. Chem.* **1974**, *38*, 163; (d) Ichihara, A.; Kimura, R.; Oda, K.; Sakamura, S. *Tetrahedron Lett.* **1976**, *17*, 4741; (e) Ichihara, A.; Kobayashi, M.; Oda, K.; Sakamura, S. *Tetrahedron* **1979**, *35*, 2861.
6. (a) Ikota, N.; Ganem, B. *J. Am. Chem. Soc.* **1978**, *100*, 351; (b) Teh-Wei Chou, D.; Ganem, B. *J. Am. Chem. Soc.* **1980**, *102*, 7987; (c) Nagata, T.; Ando, Y.; Hiroto, A. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 810; (d) Kamikubo, T.; Hiroya, K.; Ogasawara, K. *Tetrahedron Lett.* **1996**, *37*, 499 and references therein.
7. For more complex examples see: Bugni, T. S.; Abbanat, D.; Bernan, V. S.; Maiese, W. M.; Greenstein, M.; Van Wagoner, R. M.; Ireland, C. M. *J. Org. Chem.* **2000**, *65*, 7195 (Yanuthones); Sassa, T.; Ishikazi, A.; Nukina, M.; Ikeda, M.; Sugiyama, T. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 2260 (Macrophorins); Stadler, M.; Sterner, O.; Anke, H. *Z. Naturforsch., Sect. C* **1993**, *48*, 843 (Oligosporons).
8. For reviews see: Ciganek, E. *Organic Reactions* **1997**, *51*, 201; Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033; for a recent example see: Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2002**, *43*, 127.
9. (a) Kataoka, T.; Iwama, T.; Tsujiyama, S.-i.; Iwamura, T.; Watanabe, S.-i. *Tetrahedron* **1998**, *54*, 11813; (b) Shi, M.; Jiang, J.-K. *Tetrahedron* **2000**, *56*, 4793; (c) Jauch, J. *J. Org. Chem.* **2001**, *66*, 609; (d) Shi, M.; Jiang, J.-K.; Feng, Y.-S. *Org. Lett.* **2000**, *2*, 2397; (e) Kawamura, M.; Kobayashi, S. *Tetrahedron Lett.* **1999**, *40*, 1539; (f) Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965; (g) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311; (h) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510.
10. For recent examples see: Sugahara, T.; Ogasawara, K. *Synlett* **1999**, 419; Iwabuchi, Y.; Sugihara, T.; Esumi, T.; Hatakeyama, S. *Tetrahedron Lett.* **2001**, *42*, 7867.
11. (a) Matcheva, K.; Beckmann, M.; Schomburg, D.; Winterfeldt, E. *Synthesis* **1989**, 814; (b) Cambie, R. C.; Renner, N. D.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1991**, *44*, 61; (c) Miller, M. W.; Johnson, C. R. *J. Org. Chem.* **1997**, *62*, 1582.
12. (a) Kamikubo, T.; Ogasawara, K. *Heterocycles* **1998**, *47*, 69; (b) Lubineau, A.; Billault, I. *Carbohydr. Res.* **1999**, *320*, 49.
13. All new compounds were fully characterised by NMR and IR-spectroscopy and by HRMS.
14. Benkhoff, J.; Boese, R.; Klärner, G. *Liebigs Ann. Chem.* **1997**, 501.
15. Genski, T.; Macdonald, G.; Wei, X.; Lewis, N.; Taylor, R. J. K. *Synlett* **1999**, 795.
16. Pinkerton, A. A.; Schwarzenbach, D.; Stibbard, J. H. A.; Carrupt, P.-A.; Vogel, P. *J. Am. Chem. Soc.* **1981**, *103*, 2095.
17. Imagawa, T.; Uemura, K.; Nagai, Z.; Kawanisi, K. *Synth. Commun.* **1984**, *14*, 1267.
18. (a) Sekiguchi, J.; Gaucher, G. M. *Biochem. J.* **1979**, *182*, 445; (b) Ichihara, A.; Kimura, R.; Oda, K.; Moriyasu, K.; Sakamura, S. *Agric. Biol. Chem.* **1982**, *7*, 1879.