Letter

R. W. Bates et al.

Synthesis of Curvulone B Using the 2-Chlorobenzyl Protecting Group

Roderick W. Bates^{*} Kongchen Wang Guanying Zhou Dave Zhihong Kang

Svn lett

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, 637371 Singapore, Singapore roderick@ntu.edu.sg



Received: 24.11.2014 Accepted after revision: 17.12.2014 Published online: 09.02.2015 DOI: 10.1055/s-0034-1379988; Art ID: st-2014-d0964-I

Abstract A total synthesis of curvulone B has been completed using a Friedel–Crafts reaction and a highly *cis*-selective intramolecular oxa-Michael addition. The 2-chlorobenzyl protecting group was employed and found to have much greater Lewis acid stability compared to the simple benzyl group.

Key words tetrahydropyran, metathesis, Friedel–Crafts, protecting groups, cyclization

Curvulone B (1) is a *cis*-disubstituted tetrahydropyran natural product and is one of a number of related compounds isolated from a marine fungus.¹ Given our interest in the synthesis of such tetrahydropyrans by the combination of cross-metathesis and intramolecular oxa-Michael addition,^{2,3} and the fact that this chemistry gives the *cis* stereochemistry with high selectivity when the acceptor is a ketone, we set out to complete the synthesis of this compound (Scheme 1). During the course of these studies, a synthesis of curvulone B (1) was reported by Takahashi et al. using this method for THP formation.⁴ We wish to report our results in which the cross-metathesis substrate is assembled in an efficient manner, employing a novel phenol protecting group.

Our synthesis began with the economical starting material 3,5-dihydroxybenzoic acid (**4**, Scheme 2). Esterification⁵ and protection of the two phenolic hydroxy groups as their benzyl ethers, followed by reduction of the ester and chlorination with thionyl chloride gave the benzylic chloride **8a**.⁶ Palladium-catalyzed methoxycarbonylation⁷ was employed to introduce the required additional carbon atom. Although such reactions often employ elevated pressures, this was easily achieved with carbon monoxide at ambient pressure



Scheme 1 Curvulone B and its retrosynthesis

(balloon) with just 2 mol% of bis(triphenylphosphine)palladium(II) chloride as the catalyst, to give ester **9a** in 88% yield.⁸

Our initial intention was to introduce the acryloyl side chain required for metathesis by a palladium-catalyzed coupling process. While, after optimization, ester 9a could be cleanly and regioselectively iodinated α to the acetate side chain using N-iodosuccinimide (NIS) in refluxing acetonitrile, attempts to achieve a Sonogashira coupling⁹ with propargyl alcohol or a carbonylative coupling with vinyl tri*n*-butyltin¹⁰ were fruitless, returning unreacted starting material. We, therefore, resorted to a more classical C-C bond-forming technique. The Friedel-Crafts acylation of ester 9a also proceeded with complete regioselectivity to give ketone 11a, but in only 36% yield (Table 1, entry 1). The low yield was found to be due to extensive debenzylation.¹¹ Reasoning that this premature deprotection involves the Lewis acid mediated formation of a benzyl cation, we examined substituted benzyl ethers. We anticipated that an electronwithdrawing substituent would destabilize the cation and

Syn lett

R. W. Bates et al.



752

minimize the undesired deprotection pathway. Use of the 4-chlorobenzyl group^{12,13} resulted in only modest improvement (Table 1, entry 2). This substituent exerts an inductive effect. In contrast, use of an 2-chlorobenzyl protecting group resulted in an increase in yield of the Friedel-Crafts product to 89% (Table 1, entry 4).¹⁴ This is consistent with the strong dependency of the inductive effect on distance, amplifying the destabilization of the cation by placing the electron-withdrawing substituent closer to the center of positive charge. The 2-chlorobenzyl group is, therefore, more stable under Lewis acidic conditions.¹⁵ In addition, use of the 4-nitrobenzyl protecting group also resulted in a high yield of the Friedel-Crafts product (Table 1, entry 3). The mesomeric effect of the nitro group is not, of course, so attenuated by distance. Thus, both the 2-chlorobenzyl group and the 4-nitrobenzyl group proved to be much more robust than the ordinary benzyl group under Lewis acidic conditions. In all cases examined, subsequent elimination of the β -chlorine atom of ketones **11** from the side chain gave the desired enones **12** in high yield.

Table 1 Friedel–Crafts Reactions with Different Protecting Groups^a

Entry	Substrate 9	PG	Yield (%)
1	9a	Bn	36
2	9b	4-CIC ₆ H ₄ CH ₂	42
3	9c	$4-O_2NC_6H_4CH_2$	80
4	9d	2-CIC ₆ H ₄ CH ₂	89

^a Reaction at -40 °C in CH₂Cl₂ with SnCl₄ as the Lewis acid. The mixture was guenched with one equivalent of Et₃N at the same temperature.

Initial metathesis studies of enones **12** were carried out with the benzyl-protected material **12a** (Table 2). Crossmetathesis¹⁶ of the benzyl-protected substrate **12a** with TBS ether **3b**¹⁷ was found to proceed best in hexafluorobenzene (Table 2, entry 2).¹⁸ The yield using this solvent was somewhat improved over the use of toluene (Table 2, entry 1). We were unable to achieve cross-metathesis of the 4-nitrobenzyl-protected material **12d**. This failure was due to the lack of solubility of the substrate in the solvents used.

Syn<mark>lett</mark>

R. W. Bates et al.

The material is not sufficiently soluble in solvents which promote the metathesis reaction, such as toluene and hexa-fluorobenzene. Use of mixtures with more polar solvents, such as THF, appeared to inhibit metathesis. We did not, therefore, pursue studies with 4-nitrobenzyl-protected compound **12d**. In contrast, the 2-chlorobenzyl-protected material **12c** underwent cross-metathesis efficiently with TBS ether **3b** in 1,2-dichloroethane, although a quite high catalyst loading was required (Table 2, entry 6). Hexafluo-robenzene and toluene could not be used due, again, to solubility issues. 1,2-Dichloroethane was found to be the best solvent (Table 2, entries 5 and 6).

Table 2	Cross-Metathesis Reactions of Enone 12 with Alkene 3b ^a
---------	--

Entry	Substrate	PG	Solvent	Yield (%)
1	12a	Bn	toluene	62
2	12a	Bn	C_6F_6	74
3	12c	2-CIC ₆ H ₄ CH ₂	$DCE - C_6 F_6 (1:1)$	39
4	12c	2-CIC ₆ H ₄ CH ₂	$CH_2CI_2^b$	50
5	12c	2-CIC ₆ H ₄ CH ₂	DCE	55
6	12c	2-CIC ₆ H ₄ CH ₂	DCE	85°

^a Cross-metathesis reactions were carried out at 70 °C unless otherwise stated, with a continuous flow of nitrogen. The Grubbs II catalyst (5 mol% unless stated otherwise) was added in five portions at 90 minute intervals. ^b At reflux.

^c Conditions: 10 mol% of the catalyst.

Desilyation of either the benzyl compound **13a** or the 2chlorobenzyl compound **13c**, under our usual conditions with amberlyst-15 in methanol, gave the tetrahydropyrans **14a** and **14c** cleanly and directly as single *cis* diastereoisomers. In contrast, Takahashi et al., employing mildly basic conditions, obtained a mixture favoring the *trans* isomer, which required further equilibration.¹⁹ Debenzylation of either **14a** or **14c** by hydrogenation over palladium hydroxide on carbon gave the natural product **1**. The spectroscopic and chiroptical data was in good agreement with that reported: $[\alpha]_D^{21}$ –19 (*c* 0.28, EtOH) {lit.: $[\alpha]_D^{25}$ –22 (*c* 0.27, EtOH),^{1a} –15.1 (*c* 0.52, EtOH)⁴}. It is notable that, in the case of the 2-chlorobenzyl-protected material, the carbon chlorine bond was not reduced.^{20,21}

The synthesis of curvulone B has been achieved in ten steps and 39% overall yield from commercially available starting material. The efficiency of the synthesis rests upon the use of carbonylation chemistry to introduce the ester group, the metathesis–Michael strategy to introduce the *cis*-tetrahydropyran and the addition of a 2-chlorine atom to the well-known benzyl protecting group to provide robustness under Lewis acidic conditions. We believe that this protecting group will be of general use in organic synthesis.

Acknowledgment

We thank Nanyang Technological University for financial support of this work

Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379988.

References and Notes

- (a) Dai, J.; Krohn, K.; Flörke, U.; Pescitelli, G.; Kerti, G.; Papp, T.; Kövér, K. E.; Bényei, A. C.; Draeger, S.; Schulz, B.; Kurtán, T. *Eur. J. Org. Chem.* **2010**, 6928. Dothiolerone A, also known as phomopsin B, is related to this group of compounds: (b) Izuchi, Y.; Koshino, H.; Hongo, Y.; Kanomata, N.; Takahashi, S. *Org. Lett.* **2011**, *13*, 3360.
- (2) (a) Bates, R. W. Song P. *Tetrahedron* 2007, 63, 4497. (b) Bates, R. W.; Song, P. *Synthesis* 2010, 2935. (c) Bates, R. W.; Lek, T. G. *Synthesis* 2014, 46, 1731.
- (3) For reviews of intramolecular oxa-Michael addition, see:
 (a) Fuwa, H. *Heterocycles* 2012, 86, 1255. (b) Nising, C. F.; Bräse, S. *Chem. Soc. Rev.* 2012, 41, 988. (c) Larossa, I.; Romea, P.; Urpí, F. *Tetrahedron* 2008, 64, 2683. (d) Clarke, P. A.; Santos, S. *Eur. J. Org. Chem.* 2006, 2045.
- (4) Takahashi, S.; Akita, Y.; Nakamura, T.; Koshino, H. *Tetrahedron: Asymmetry* **2012**, *23*, 952.
- (5) Denmark, S. E.; Regens, C. S.; Kobayashi, T. J. Am. Chem. Soc. 2007, 129, 2774.
- (6) Comber, M. F.; Sargent, M. V.; Skelton, B. W.; White, A. H. J. Chem. Soc., Perkin Trans. 1 1989, 441.
- (7) Schoenberg, A.; Bartoletti, I.; Heck, R. F. J. Org. Chem. **1974**, 39, 3318.
- (8) The alternative would be three steps: substitution with cyanide, hydrolysis, and esterification; see ref. 6.
- (9) Chincilla, R.; Nájera, C. Chem. Rev. 2007, 107, 874.
- (10) Goure, W. F.; Wright, M. E.; Davis, P. D.; Labadie, S. S.; Stille, J. K. J. Am. Chem. Soc. **1984**, 106, 6417.
- (11) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. J. Org. Chem. **1989**, 54, 1346.
- (12) 4-Bromo- and 4-chlorobenzyl ethers have been found to be more stable to TFA than simple benzyl ethers: (a) Yamashiro, D. *J. Org. Chem.* **1977**, *42*, 523. 4-Chloro, 4-iodo, and 2-bromobenzyl ethers have been employed in carbohydrate chemistry. The groups were cleaved by amination, and considered to be of 'comparable chemical inertness' to simple benzyl ethers: (b) Plante, O. J.; Buchwald, S. L.; Seeburger, P. H. *J. Am. Chem. Soc.* **2000**, *122*, 7148.
- (13) The yield obtained using the 4-fluorobenzyl group was similar.
- (14) 2-Halobenzyl ethers, cleaved by hydrogenolysis, have been reported in the patent literature: (a) Cao, S. X.; Feng, J.; Imaeda, Y.; Gwaltney, S. L.; Hosfield, D. J.; Takakura, N.; Tang, M. US 2007197532 A1, **2007**. (b) Alihodzic, S.; Bosnar, M.; Culic, O.; Erakovic Haber, V.; Hutinec, A.; Jelic, D.; Kragol, G.; Marjanovic, N.; Marusic-Istuk, Z.; Ribic, M.; Vela, V. US 2008221046 A1, **2008**.
- (15) Such ethers are still labile to strong Lewis acids, such as tin tetrachloride: (a) Li, N.-S.; Lu, J.; Piccirilli, J. A. Org. Lett. 2007, 9, 3009. Or zinc chloride: (b) Huston, R. C.; Gyorgy, H. H. J. Am. Chem. Soc. 1950, 72, 4171.

Syn lett

R. W. Bates et al.

- (16) Connon, S. J.; Blechert, S. Angew. Chem. Int. Ed. 2003, 42, 1900.
- (17) Takahashi et al. reported that cross-metathesis does not proceed with the unprotected alcohol **3a** (ref. 4). We also found this to be the case. We propose that an unreactive chelate forms.
- (18) (a) Samojłowicz, C.; Bieniek, M.; Pazio, A.; Makal, A.; Woźniak, K.; Poater, A.; Cavallo, L.; Wójcik, J.; Zdanowski, K.; Grela, K. *Chem. Eur. J.* 2011, *17*, 12981. For a helpful discussion of metathesis conditions, see: (b) Bieniek, M.; Michrowska, A.; Usanov, D. L.; Grela, K. *Chem. Eur. J.* 2008, *14*, 806.
- (19) For the specific production of *trans*-THPs in this way, see:
 (a) Banwell, M. G.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. J. Chem. Soc., Perkin Trans. 1 1996, 967. (b) Banwell, M. G.; Bissett, B. D.; Bui, C. T.; Pham, H. T. T.; Simpson, G. W. Aust. J. Chem. 1998. 51, 9.
- (20) 2-Chlorotoluene was detected in the crude reaction mixture.
- (21) A solution of compound **14c** (69 mg, 0.128 mmol) in EtOAc (5 mL) containing 20% Pd(OH)₂ on carbon (30 mg) was stirred overnight under hydrogen (balloon). The mixture was filtered through Celite and concentrated. Purification by flash chromatography on silica eluting with 50% EtOAc-hexane gave **1** as a colorless oil (42 mg, 81%). $[\alpha]_D^{21}$ –19 (*c* 0.28, EtOH) {lit.:^{1a,4} $[\alpha]_D^{25}$ –22 (*c* 0.27, EtOH), –15.1 (*c* 0.52, EtOH)]. ¹H NMR (400 MHz, CDCl₃): δ = 9.77 (s, 1 H), 6.27 (d, *J* = 2.3 Hz, 1 H), 6.21 (d, *J* = 2.3 Hz, 1 H), 4.13 (m, 1 H), 3.94 (d, *J* = 16.5 Hz, 1 H), 3.70 (s, 3 H), 3.57 (m, 1 H), 3.51 (d, *J* = 16.5 Hz, 1 H), 3.30 (dd, *J* = 14.2, 10.3 Hz, 1 H), 2.57 (dd, *J* = 14.3, 3.2 Hz, 1 H), 1.84 (m, 1 H), 1.67 (m, 1 H), 1.63 (m, 1 H), 1.57 (m, 1 H), 1.44 (m, 1 H), 1.27 (m, 1 H), 1.17 (d, *J* = 5.9 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): *J* = 204.24, 172.44, 159.51, 159.41, 135.77, 120.88, 111.73, 104.05, 77.90, 74.87, 52.10, 49.04, 39.74, 32.68, 30.73, 23.11, 21.50.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.