Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1363-1366, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(96)02494-X

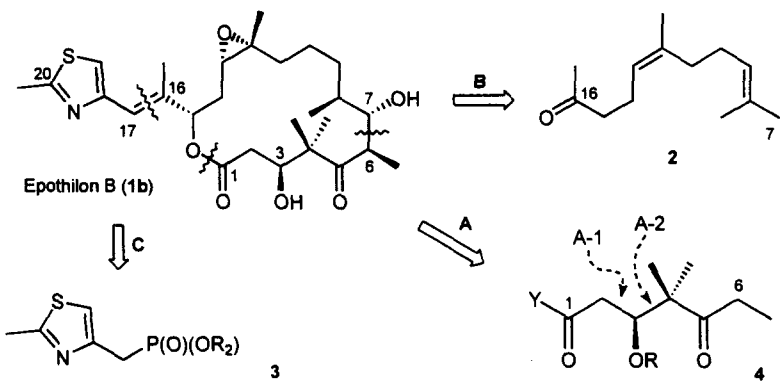
The Chromium-Reformatsky Reaction: Asymmetric Synthesis of the Aldol Fragment of the Cytotoxic Epothilons from 3-(2-Bromoacyl)-2-oxazolidinones

Tobias Gabriel, Ludger Wessjohann*

Institut für Organische Chemie, Ludwig-Maximilians-Universität München,
Karlstraße 23, D-80333 München (Germany)

Abstract: In a two step, one pot reaction of 4-benzyl oxazolidinone, 2-bromoacetyl halide, chromium dichloride and a suitable 3-oxo-aldehyde derivative the C1-C6-Me - fragment of epothilons is available in its correct oxidation state and enantiomeric form. Compared to common methods, the chromium-Reformatsky variation preferentially yields the opposite diastereomers and gives improved chemo- and diastereoselection.

The epothilons (**1**) are a recently discovered group of macrocyclic lactones with a taxol-like mitose inhibition profile.[1,2] Although in vivo studies have not yet been published, the compounds appear to be at least as active as taxoids, but provide much better solubility and access. Accordingly the molecule quickly became a prime target of synthetic chemists.[2-6] As with taxol,[7] however, it finally may be more important to synthesize derivatives for structure-activity relationships, a task which is easier done synthetically then by fermentation.[2]



Scheme 1. Strategic Analysis of Epothilon B

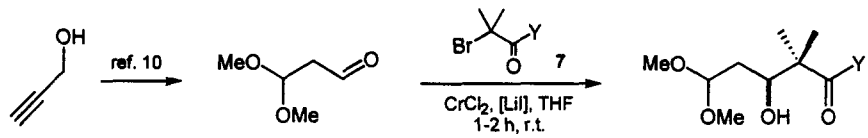
A retro-analysis of epothilons reveals three fragments (Scheme 1): (A) An "aldol" fragment C1-C6 (**4**); (B) A "prenyl" fragment C7-C16; which biosynthetically may rather be polyketide-derived, but synthetically suggests commercial nerol/geraniol or nerylacetone (**2**) as suitable precursors for a C7-aldehyde - at least for

Fax: Int. +(89) 5902-483 • E-mail: law@org.chemie.uni-muenchen.de

epothilone B (**1b**); and (C) a heteroaromatic fragment C17-C20, already available as **3**.[5] In this paper we focus on the asymmetric synthesis of aldol fragments of type **4** (C1-C6-Me) by an improved Reformatsky-type aldol reaction.

Recently we introduced the chromium(II)-mediated Reformatsky reaction as alternative to conventional heterogeneous methods.[8] They reproducibly yield aldol products without the necessity of activation even in microscale reactions. Among the many advantages of the chromium variation are the excellent chemoselectivity towards aldehydes and, compared to zinc ester enolates, an inversed simple diastereoselectivity. The reaction also allows access to quarternary centers prone to retro-aldolization, a drawback of many base catalyzed aldolizations. Such a retro-cleavage will be facile at A-2, yielding stabilized and less strained products which rather follow other reaction paths after cleavage. With chromium(III)-enolates, however, this should not be a problem.[8]

Fragment **1** offers two sites for aldol couplings A-1 and A-2 (Scheme 1). Both disconnections require β-induction. We concentrated on Evans' 4-benzyl-oxazolidinones as chiral auxiliaries, readily available as both enantiomers. Disconnection at A-1 would require chemoselective reaction at the aldehyde, and induction from an acetyl-derived anion. The latter are known to give only moderate diastereomeric excesses (de ≈ 4 - 74%).[9]

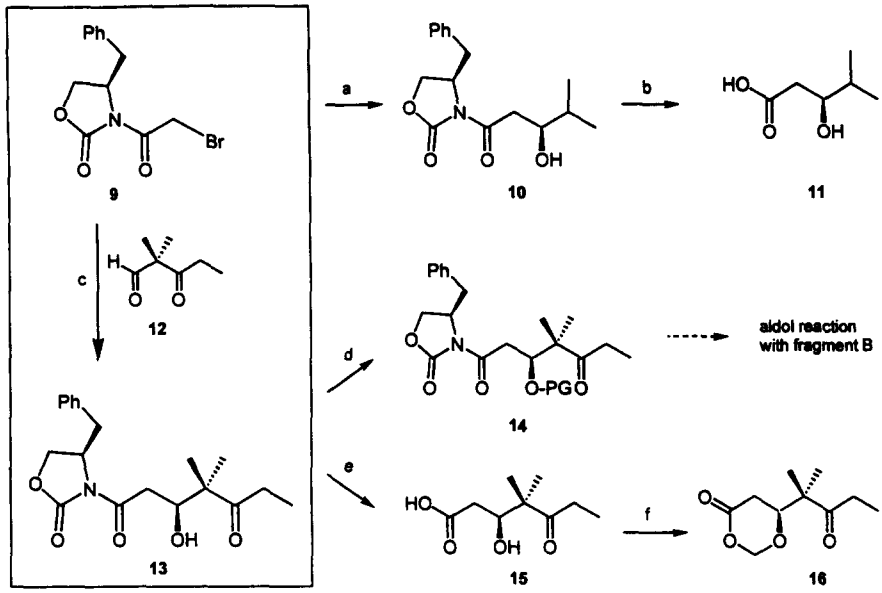


5 **6** **8**

Scheme 2. Connection A-2: **7, 8 a**: Y = OMe (66%); **b**: Y = (*R*)-4-benzyl-oxazolidinon-3-yl (76%, > 99 : 1)

Thus a route connecting at A-2 was chosen initally (Scheme 2). It allows free selection of the protective group at C1. Considering basic reaction conditions later and a similarity to the model system investigated by Meyer, Kalesse et al.[6] an acetal group was chosen. 3,3-Dimethoxypropanal (**6**), available from propargyl alcohol (**5**),[10] reacts with methyl 2-bromoisobutyrate (**7a**) and chromium dichloride (THF, cat. LiI, 1 h) to give **8a** (66%).[11] The same reaction was conducted with bromide **7b**, which is available in one step from commercial 2-bromoisobutyric bromide (91%) and lithium (*S*)-4-benzyl-oxazolidinone (91%). The isolated yield increased to 76% of **8b** as a single diastereomer according to NMR and GC (de > 99%).[12] Further conversion to the corresponding ethylketone (**8c**, Y = Et) may be achieved by published procedures.[13]

At this stage, however, we learned from our ongoing systematic study that 3-(2-bromoacetyl)-oxazolidones in the chromium-Reformatsky reaction behave much better than the corresponding boron-, zinc- or lithium-enolates. *R*-**9**, obtained in 97% yield (cf. **7b**), reacted with isobutyraldehyde to give 96% (R)/S-diastereomer (**10**) and 4% (S)/S (91% chemical yield). The absolute configuration of the new stereocenter was established by conversion to the known acid **11** (96%).[14] Interestingly chromium(III) not only quantitatively improved the induction, the predominant diastereomer also has the opposite relative stereochemistry to that obtained with most other metal ions (e.g. Zn, Li).[9] The formation of the 3-(2-bromoacyl)-2-oxazolidinones and the chromium-Reformatsky reaction may also be run in one pot without problems.



Scheme 3. Connection at A-1: a) 2-Methylpropanal, $CrCl_2$, cat. LiI, THF, r.t., 5h, 91% (96 : 4); b) H_2O_2, LiOH, THF/H_2O, 0°C, 1 h, 96%; c) **12**, cf. (a), 63%; d) PG = *t*-$BuMe_2Si$: TBDMS-OTf, lutidine, CH_2Cl_2, 0°C, 1.5 h (93%); PG = 4-NO_2-C_6H_4CO: 4-nitrobenzoyl chloride, DMAP, pyH, r.t., 3 d, 69%; e) cf. (b) 92%; f) $(H_2CO)_n$, cat. TsOH, mol. sieve 3 Å, CH_2Cl_2, rfx, 2 h, 98% (92 : 8).

With ketoaldehyde **12**, readily available from isobutyraldehyde and propionyl chloride,[15] Reformatsky product **13** was formed chemoselectively (yield: 63%, not optimized). Liberation of acid **15**[16] by hydrogen peroxide and bis-protection with formaldehyde to **16** is achieved in over 90% combined yield. Dioxanone **16** according to chiral phase GC has a 92 : 8 ratio of enantiomers.[16] Alternatively **13** can be protected as *p*-nitrobenzoyl ester (**14a**: 69%) or TBDMS ether (**14b**: 93%).[16] The latter is expected to have similar induction properties in a C6-C7 aldol reaction as the corresponding C1-ether.[4,6,17]

Although the chromium-Reformatsky approach A-2 provides excellent induction (> 99 : 1), we consider route A-1 to be more practical overall. The ready availability of aldehyde **12** with the ethyl-ketone moiety already attached warrants a possible separation of diastereomers or further improvements of the 92 : 8 ratio through variation of reaction conditions or with other auxiliaries.

In summary, the chromium-Reformatsky-approach provides by far the shortest enantioselective route to the aldol fragment A (**8c**, **13-16**) of epothilons available to date (2 steps). In general the method allows greatly improved direct β-inductions from Evans enolates not possessing a prochiral C-α and access to the opposite diastereomers and thus enantiomers.

Acknowledgements: We wish to thank Prof. Dr. W. Steglich and the Degussa AG for support and generous gifts of chemicals, respectively.

References and Notes

1. Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem.* **1996,** *108,* 1671-1673; *Angew. Chem. Int. Ed. Engl.* **1996,** *35,* 1567-1569; Gerth, K.; Bedorf, N.; Höfle, G.; Irschik, H.; Reichenbach, H. *J. Antibiot.* **1996,** *49,* 560-563; tubulin-stabilization: Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995,** *55,* 2325-2333.
2. Reviews: Schinzer, D. *Eur. Chem. Chron.* **1996,** *1,* 7-10; Wessjohann, L. *Angew. Chem.* **1997,** submitted.
3. Balog, A.; Meng, D.; Kamenecka, T.; Bertinato, P.; Su, D.-S.; Sorensen, E. J.; Danishefsky, S. J. *Angew. Chem.* **1996,** *108,* in press.
4. Nicolaou, K. C.; He, Y.; Vourloumis, D.; Vallberg, H.; Yang, Z. *Angew. Chem.* **1996,** *108,* 2554-2556; *Angew. Chem. Int. Ed. Engl.* **1996,** *35,* 2399-2401.
5. Schinzer, D.; Limberg, A.; Böhm, O. M. *Chem. Eur. J.* **1996,** *2,* 1477-1482.
6. Claus, E.; Pahl, A.; Jones, P. G.; Meyer, H. M.; Kalesse, M. *Tetrahedron Lett.* **1997,** adjacent publication.
7. Nicolaou, K. C.; Dai, W.-M.; Guy, R. K. *Angew. Chem.* **1994,** *106,* 38-69; *Angew. Chem. Int. Ed. Engl.* **1994,** *33,* 45; Wessjohann, L. *Angew. Chem.* **1994,** *106,* 1011-1013; *Angew. Chem. Int. Ed. Engl.* **1994,** *33,* 959-961.
8. Wessjohann, L.; Wild, H. *Synthesis* **1997,** accepted; Wessjohann, L. A.; Gabriel, T. *J. Org. Chem.* **1997,** submitted; Gabriel, T.; Wessjohann, L. Aldol Reactions Made Irreversible by an Intrinsic Kinetic Quench: The Chromium Reformatsky Reaction. In *11th International Conference On Organic Synthesis (ICOS-11);* KNCV and IUPAC Eds.; H. Hiemstra (Amsterdam Institute of Molecular Studies): Amsterdam, 1996; p. 317; Wessjohann, L.; Mühlbauer, A. Chrom(II)-vermittelte Reaktionen vom Reformatsky Typ: Lösungsmitteleinfluß, Regio- und Diastereoselektivität. In *24. GDCh-Hauptversammlung Hamburg;* GDCh Ed.; VCH: Weinheim, 1993; p. 502.
9. Braun, M. Formation of C-C Bonds by Addition of Enolates to Carbonyl Groups: α-Unsubstituted Amide and Imide Enolates. In *(Houben-Weyl: Methods in Organic Chemistry) Stereoselective Synthesis;* Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. Eds.; Georg Thieme Verlag: Stuttgart, 1995; Vol. E21b; pp. 1656-1660; Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev.* **1996,** *96,* 835 - 875.
10. Sauer, J. C.; Sheehan, J. C.; Gilmont, E. R. *Org. Synth., Coll. Vol.* **1963,** *4,* 813-815; Skoldinov, A. P.; Arendaruk, A. P.; Godzhello, T. M. *J. Org. Chem. USSR (Engl. Transl.)* **1970,** *6,* 421-426. CAUTION, explosive hazard from propargyl aldehyde, e. g. with bases!
11. Cf. also Kende, A. S.; Kawamura, K.; Orwat, M. J. *Tetrahedron Lett.* **1989,** *30,* 5821-5824.
12. By analogy to similar compounds in this series *S*-stereochemistry can be assumed for C-β.
13. Cf. Evans, D. A.; Bender, S. L. *Tetrahedron Lett.* **1986,** *27,* 799-802.
14. Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981,** *103,* 3099-3111.
15. Inukai, T.; Yoshizawa, R. *J. Org. Chem.* **1967,** *32,* 404-407.
16. Selected data of compounds. **14**: ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ = 0.09 (s, 3H, CH_3Si), 0.12 (s, 3H, CH_3Si), 0.88 (s, 9H, $(CH_3)3$, 0.99 (t, J = 7.7 Hz, 3H, $C\underline{H}_3CCH_2$), 1.14 (s, 3H, CH_3C), 1.17 (s, 3H, CH_3C), 2.55 (q, J = 7.7 Hz, 2 H, $C\underline{H}_2CH_3$), 2.69 (dd, J = 14.9 Hz, J = 11.4 Hz, 1H, $C\underline{H}_2CHN$), 3.05 (d, J = 5.7 Hz, 2H, CH_2COSi), 3.38 (dd, J = 14.9 Hz, J = 3.7 Hz, 1H, $C\underline{H}_2CHN$), 4.11-4.21 (m, 2H, CH_2O), 4.60-4.68 (m, 1H, CHN), 4.72 (t, J = 5,7 Hz, 1 H, CHOSi), 7.09-7.24 (m, 5H, ar.); ^{13}C-NMR (75.5 MHz, $CDCl_3$, TMS): δ = -4.9, -4.2, 7.7, 18.2, 19.4, 22.2, 26.0, 31.5, 38.1, 40.7, 52.8, 55.4, 66.2, 71.9, 127.3, 129.0, 129.4, 135.5, 153.5, 171.3, 215.7; MS (EI, 70 eV): m/z (%) = 461 (M^+), 404, 362, 348, 330, 304, 276, 252, 227, 185, 157, 145, 117, 91.
15: ^{1}H-NMR (300 MHz, $CDCl_3$, TMS): δ = 1.03 (t, J = 8.0 Hz, 3 H, CH_3), 1.15 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 2.63 -2.89 (m, 4 H,CH_2, CH_2), 4.21 (dd, J = 10.4 Hz, J = 2.4 Hz, 1H, CH), 5.85 (br, OH); ^{13}C-NMR (75.5 MHz, $CDCl_3$, TMS): δ = 8.2, 20.0, 22.1, 31.7, 37.0, 51.2, 73.2, 177.5, 217.3; MS (CI, isobutane): m/z (%) = 189 (MH^+), 171, 153, 129, 101, 100. 83, 71. EA: C ± 0.39, H ± 0.11; $[\alpha]_D^{20}$= -26.1 (c=2.9; $CHCl_3$) (for the (*R*)-enantiomer, assignment deducted from **11**). Analysis of the enantiomeric ratio was possible with derivative **16** by GC on 25 m 2,6-pentyl-4-butyryl-β-cyclodextrin (70% in OV 1701). We wish to thank Prof. Dr. W. König, Hamburg, for his support.
17. Evans, D. A.; Clark, S. J.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990,** *112,* 866-868.

(*Received in Germany* 26 *November* 1996; *accepted* 17 *December* 1996)