Notes

A Cobalt−Phosphine Complex Directed Reformatsky Approach to a Stereospecific Synthesis of the Dolastatin 10 Unit Dolaproine (Dap)[1]

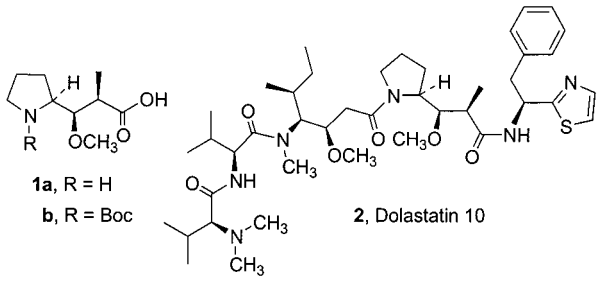
George R. Pettit* and Matthew P. Grealish

Cancer Research Institute and Department of Chemistry and Biochemistry, Arizona State University, Tempe, Arizona 85287-2404

bpettit@asu.edu

Received May 24, 2001

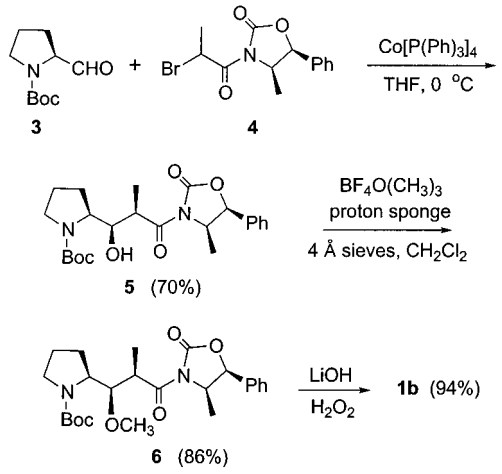
The well-known Reformatsky reaction for forming carbon−carbon bonds has been undergoing extensive improvements by replacing the classic zinc-based procedure[2] with, e.g., germanium[3] or samarium[4] metal-promoted reactions. The activated germanium[3]-catalyzed asymmetric Reformatsky reaction between enantiomerically pure oxazolidinones and aldehydes has been found to afford good diastereoselectivity with (1*S*,2*R*)-2-amino-1,2-diphenylethanol-derived precursors. Prior to availability of the germanium/chiral oxazolidinone/aldehyde procedure,[3] we began to evaluate an analogous reaction with a tetrakis(triphenylphosphine)cobalt(0)[5]-directed asymmetric Reformatsky reaction as a new stereospecific route to the dolaproine (**1a**, Dap) unit of dolastatin 10 (**2**)[6] now in Phase II human cancer clinical trials.[7]



Previously we established the absolute configuration of the three-chiral-centered amino acid unit dolaproine (**1a**) by total syntheses[6a] of dolastatin 10 (**2**) and by an X-ray crystal structure determination of (6*R*)-isodolastatin 10.[6b] Our initial synthesis of Dap involved using the magnesium enolate of a chiral propionate in an aldol reaction. That led to all four diastereoisomers in varying yields.[8] Subsequently, we greatly improved the aldol approach by condensing *S*-prolinal with a chiral oxazolidinone using dibutylboron triflate to direct the stereochemical course.[9] Other boron-catalyzed aldol approaches to Dap have also been described.[10] Because of the increasing need for Dap to meet clinical supply requirements for dolastatin 10 (**1**) and our SAR studies[11] of this quite remarkable sea hare constituent, we undertook a cobalt−phosphine complex mediated asymmetric Reformatsky approach to Boc-Dap (**1b**).

The Orsini[5] cobalt−phosphine Reformatsky-type reactions of α-halocarbonyl derivatives with aldehydes or ketones to give secondary and tertiary alcohols offers several advantages over the classic zinc-mediated Reformatsky reaction, the most notable being milder conditions and higher yields of addition products.

Cobalt−triphenylphosphine-promoted Reformatsky reaction between *N*-Boc-S-prolinal[9] (**3**) and 3-(2-bromopropionyl)-4*R*-methyl-5*S*-phenyloxazolidin-2-one (**4**)[9,12] stereoselectively furnished the *β*-hydroxy amide **5** in 70% yield. Subsequent *O*-methylation of alcohol **5** with trimethyloxonium tetrafluoroborate[13] led to methyl ether **6** in 86% yield. Hydrolysis of the chiral auxiliary with



hydrogen peroxide and lithium hydroxide provided Boc-(2*S*,2′*R*,3′*R*)-Dap (**1b**) in 94% yield. Attempts to cleave

* To whom correspondence should be addressed.

(1) Contribution 475 in the series Antineoplastic Agents: for part 474 refer to Bai, R.; Verdier-Pinard, P.; Sausville, E. A.; Pettit, G. R.; Bates, R. B.; Hamel E. *Mol. Pharm.* **2000**, in press.

(2) (a) Pini, D.; Uccello-Barretta, G.; Mastantuono, A.; Salvadori, P. *Tetrahedron* **1997**, *53*, 6065. (b) Rathke, M. W. In *Organic Reactions*; Dauben, W. G. et al., Eds.; John Wiley & Sons: New York, 1975; Vol. 22, pp 423−449.

(3) Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. *J. Org. Chem.* **1998**, *63*, 691.

(4) (a) Fukuzawa, S.; Matsuzawa, H.; Yoshimitsu, S. *J. Org. Chem.* **2000**, *65*, 1702−1706. (b) Ichikawa, S.; Shuto, S.; Minakawa, N.; Matsuda, A. *J. Org. Chem.* **1997**, *62*, 1368. (c) Shen, Z.; Zhang, J.; Zou, H.; Yang, M. *Tetrahedron Lett.* **1997**, *38*, 2733.

(5) (a) Orsini, F.; Pelizzoni, T.; Pulici, M.; Vallarino, L. M. *J. Org. Chem.* **1994**, *59*, 1−3. (b) Orsini, F.; Pulici, M. Highlights on Recent Advancement on Reformatsky-Type Reactions: the Cobalt Approach. In *Trends in Organometallic Chemistry*; Research Trends Ed., Trivandrum: India, 1994; Vol. 1, pp 625−667. (c) Orsini, F. *Tetrahedron Lett.* **1998**, *39*, 1425. (d) Orsini, F. *J. Org. Chem.* **1997**, *62*, 1159.

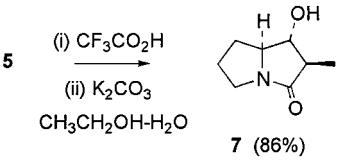
(6) (a) Pettit, G. R.; Srirangam, J. K.; Singh, S. B.; Williams, M. D.; Herald, D. L.; Barkóczy, J.; Kantoci, D.; Hogan, F. *J. Chem. Soc., Perkin Trans. 1* **1996**, 859. (b) Pettit, G. R.; Srirangam, J. K.; Herald, D. L.; Hamel, E. *J. Org. Chem.* **1994**, *59*, 6127. (c) Pettit, G. R. The Dolastatins. In *Progress in the Chemistry of Organic Natural Products*; Springer-Verlag: New York, 1991; No. 57, pp 153−195.

(7) Madden, T.; Tran, H. T.; Beck, D.; Huie, R.; Newman, R. A.; Pusztai, L.; Wright, J. J.; Abbruzzese, J. L. *Clin. Cancer Res.* **2000**, *6*, 1293.

(8) Pettit, G. R.; Singh, S. B.; Herald, D. L.; Lloyd-Williams, P.; Kantoci, D.; Burkett, D. D.; Barkóczy, J.; Hogan, F.; Wardlaw, T. R. *J. Org. Chem.* **1994**, *59*, 6287.

10.1021/jo010530t CCC: $20.00
Published on Web 11/09/2001

the oxazolidinone (**5**) prior to *O*-methylation leads to byproducts and makes purification more difficult.[9] The stereochemistry of the Reformatsky product was further confirmed by conversion[9] to the known[9] pyrrolizidinone derivative **7**. While the Reformatsky reaction (70% yield) was certainly competitive with the boron-directed aldol approach[9] (60% yield), the cobalt−phosphine complex method was also more convenient experimentally to perform and the results more reproducible.



No attempt was made to determine the enolate geometry or the oxidation state of the cobalt species in the present Reformatsky reactions. However, on the basis of the absolute configuration of the product, diastereofacial selection was considered to occur in the same manner as in the aldol reaction of boron enolates[9,10c] derived from enantiomerically pure 2-oxazolidinones.[14] Thus, the observed syn/anti selectivity of the present Reformatsky reaction can be interpreted in terms of the Zimmerman−Traxler model,[15] in which the geometry of the enolate correlates with the relative configuration of the products.

In summary, the cobalt−triphenyl phosphine complex mediated Reformatsky synthesis of the Dap (**1a**) unit of dolastatin 10 (**2**) was found to proceed smoothly under mild and neutral conditions. In general, the new synthesis was very easy to implement and, for example, did not require anhydrous solvents, a temperamental aldol boron enolate, or very low reaction temperature.[9] The method therefore represents a valid improvement to the existing procedures for synthesizing dolaproine.

Experimental Section

All solvents were redistilled. Anhydrous cobalt(II) chloride was heated at 120−150 °C for 2 h prior to use. Magnesium (turnings) was activated by grinding the metal in a mortar and treatment with a solution of 1,2-dichloroethane in tetrahydrofuran (THF), followed by washing with THF. Both the course and products from reactions were monitored by thin-layer chromatography using Analtech silica gel GHLF uniplates. All reactions were carried out under an inert atmosphere. Solvent extracts of aqueous solutions were dried over anhydrous sodium sulfate unless otherwise noted. Flash column chromatography was performed using silica gel (230−400 mesh ASTM).

Melting points were recorded employing an Electrothermal 9100 digital melting point apparatus and are uncorrected. The IR spectra were obtained using a Mattson FTIR model 2020 instrument. Low-resolution mass spectral data were collected using a Varian MAT 312 instrument (EIMS). The high-resolution FAB spectra were obtained employing a Kratos MS-50 mass spectrometer at the Midwest Center for Mass Spectrometry, University of Nebraska, Lincoln, NE. All ^{1}H and ^{13}C NMR spectra were determined using a Varian Gemini 300 MHz instrument with $CDCl_3$ (TMS internal reference) as solvent unless otherwise noted. Elemental analyses were determined by Galbraith Laboratories Inc., Knoxville, TN.

Preparation of the Cobalt−Triphenylphosphine Complex.[5] Activated magnesium turnings (0.5 g), anhydrous cobalt(II) chloride (0.13 g, 1 mmol), and triphenylphosphine (1.05 g, 4 mmol) were added to THF (5 mL). The mixture was stirred until the blue color turned to dark-brown. Immediately before use, the supernatant was transferred by syringe to the reaction flask.

(4*R*,5*S*,2′*R*,3′*R*,2″*S*)-3-[3′-(*N*-*tert*-Butoxycarbonyl-2″-pyrrolidinyl)-3′-hydroxy-2′-methylpropanoyl)-4-methyl-5-phenyl-2-oxazolidinone (5). To a solution cooled to 0 °C containing 3-(2-bromopropionyl)-4*R*-methyl-5*S*-phenyloxazolidin-2-one (**4**, 0.31 g, 1 mmol) in anhydrous THF (5 mL) was added (dropwise over 30 min) the cobalt−triphenylphosphine complex (1 mmol). Next N-Boc-L-prolinal (**3**, 0.20 g, 1 mmol)[8] was added to the dark brown solution and stirring was continued for 2 h. The reaction mixture was poured into cold 0.1 N HCl and extracted with ethyl acetate and the solvent evaporated under reduced pressure. The crude product was separated by flash column chromatography (4:1 hexane−ethyl acetate) to afford the title compound as a colorless foam (0.30 g, 70%): $[\alpha]^{25}_D$ −9.77° (*c* 1.73, $CHCl_3$); lit[10c] $[\alpha]^{23}_D$ −10.2° (*c* 1.0, $CHCl_3$); EIMS *m*/*z* 432 (M^+), 414, 359, 262, 170, 114, 70; IR (KBr, cm^{-1}) ν_{max} 3445, 2978, 1782, 1694, 1393, 1196, 1121; ^{1}H NMR δ 7.44−7.29 (5H, m), 5.67 (1H, d, J = 7.2 Hz), 4.76 (1H, p, J = 3.9 Hz), 3.97−3.92 (2H, m), 3.91−3.85 (1H, m), 3.54−3.46 (1H, m), 3.26−3.19 (1H, m), 2.15 (1H, bs), 1.93−1.79 (3H, m), 1.51 (1H, s), 1.50−1.47 (9H, s), 1.33 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz).

(4*R*,5*S*,2′*R*,3′*R*,2″*S*)-3-[3′-(*N*-*tert*-Butoxycarbonyl-2″-pyrrolidinyl)-3′-methoxy-2′-methylpropanoyl)-4-methyl-5-phenyl-2-oxazolidinone (6). To a flask containing alcohol **5** (0.36 g, 0.84 mmol) and molecular sieves (4 Å, 0.37 g) was added anhydrous dichloromethane (10 mL), and the mixture was cooled to 0 °C. Proton sponge (0.47 g, 2.2 mmol, 2.6 equiv) and trimethyloxonium tetrafluoroborate (0.31 g, 2.1 mmol, 2.5 equiv) were added to the clear colorless liquid at 0 °C. The solution slowly turned a turbid tan-yellow and was stirred for 48 h at r.t. The yellow cloudy solution was filtered and the solvent evaporated under reduced pressure to a yellow solid. The solid was separated by flash chromatography (3:1 hexane−ethyl acetate) to afford a colorless oil (0.32 g, 86%): $[\alpha]^{25}_D$ −44.9° (*c* 0.53 CH_3OH); EIMS *m*/*z* 446 (M^+), 414, 373, 331, 276, 213; IR (KBr, cm^{-1}) ν_{max} 2978, 1782, 1694, 1393, 1196, 1121; ^{1}H NMR (400 MHz) δ 7.42−7.29 (5H, m), 5.63 (1H, d, J = 7.2 Hz), 4.71 (1H, m), 3.93 (2H, m), 3.84 (2H, m), 3.47 (3H, s, OCH_3), 3.20 (1H, m), 1.96 (2H, m), 1.78 (2H, m), 1.50 (9H, s), 1.30 (3H, d, J = 6.8 Hz), 0.88 (3H, d, J = 6.8 Hz).

(2*R*,3*R*,2′*S*)-3-(*N*-*tert*-Butoxycarbonyl-2′-pyrrolidinyl)-3-methoxy-2-methylpropanoic Acid (1b, Boc-dolaproine). To a solution of oxazolidinone amide protected Dap (0.14 g, 0.32 mmol) in THF (10 mL) at 0 °C was added hydrogen peroxide (0.14 g of 30% 1.2 mmol, 3.8 equiv) over 10 min. Lithium hydroxide monohydrate (0.022 g, 0.53 mmol, 1.7 equiv) was added and the resulting turbid white mixture stirred for 3 h. To the solution was added sodium sulfite (0.16 g, 1.3 mmol, 4.0 equiv) and stirring continued for 18 h at 0 °C to r.t. The reaction mixture was concentrated and extracted with dichloromethane to remove the oxazolidinone auxiliary. The aqueous layer was acidified to pH 2 and extracted with ethyl acetate, and the combined extract was washed with water and evaporated in vacuo to give carboxylic acid **1b** as a colorless oil (0.86 g, 94%): $[\alpha]^{25}_D$ −57° (*c* 2.08, CH_3OH); lit.[8] $[\alpha]_D$ −61.4° (*c* 0.5, CH_3OH); EIMS *m*/*z* 287 (M^+), 255, 214, 170, 114, 70; IR (KBr, cm^{-1}) ν_{max} 3084, 2978, 2938, 2884, 1736, 1696, 1402, 1167, 1099; ^{1}H NMR (500 MHz, CD_3CN, 50 °C) δ 3.80 (2H, m), 3.44 (1H, m), 3.39 (3H, s, OCH_3), 3.16 (1H, m), 2.47 (1H, m), 1.96−1.82 (4H, m), 1.72 (1H, m), 1.44 (9H, s), 1.18 (3H, d, J = 7 Hz).

(9) Pettit, G. R.; Burkett, D. D.; Barkóczy, J.; Breneman, G. L.; Pettit, W. E. *Synthesis* **1996**, 719.

(10) (a) Tomioka, K.; Kamai, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 2395. (b) Roux, F.; Maugras, I.; Poncet, J.; Niel, G.; Jouin, P. *Tetrahedron* **1994**, *50*, 5345. (c) Shioiri, T.; Hayashi, K.; Hamada, Y. *Tetrahedron* **1993**, *49*, 1913.

(11) (a) Pettit, G. R.; Srirangam, J. K.; Barkoczy, J.; Williams, M. D.; Boyd, M. R.; Hamel, E.; Pettit, R. K.; Hogan, F.; Bai, R.; Chapuis, J.-C.; McAllister, S. C.; Schmidt, J. M. *Anti-Cancer Drug Design* **1998**, *13*, 243. (b) Pettit, G. R.; Srirangam, J. K.; Barkoczy, J.; Williams, M. D.; Durkin, K. P. M.; Boyd, M. R.; Bai, R.; Hamel, E.; Schmidt, J. M.; Chapuis, J.-C. *Anti-Cancer Drug Design* **1995**, *10*, 529.

(12) Song, C. E.; Lee, S. G.; Lee, K. C.; Kim, I. O.; Jeong, J. H. *J. Chromatogr. A* **1993**, *654*, 303.

(13) Diem, M. J.; Burow, D. F.; Fry, J. L. *J. Org. Chem.* **1990**, *42*, 180.

(14) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83. (c) Yan, T. H.; Tan, C. W.; Lee, H. C.; Lo, H. C.; Huang, T. Y. *J. Am. Chem. Soc.* **1993**, *115*, 2613.

(15) Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920.

(1*R*,2*R*,8*S*)-Hexahydro-1-hydroxy-2-methyl-3*H*-pyrrolizin-3-one (7). To a flask containing Reformatsky product **5** (1.03 g, 2.4 mmol) was added trifluoracetic acid (10 mL). The mixture was stirred at room temperature for 20 min and concentrated in vacuo. The remaining solvent was codistilled with toluene. The resulting pink oil was dissolved in ethanol−water (1:2, 30 mL) and cooled to 0 °C. Potassium carbonate (0.45 g, 3.3 mmol) was added, and the mixture was stirred for 1.5 h, concentrated in vacuo, and extracted with dichloromethane. The combined organic extract was concentrated, and the resulting yellow oil was separated by flash column chromatography (1:5:10 ethanol−ethyl acetate−dichloromethane) to afford the chiral oxazolidinone first and then lactam **7** (0.32 g, 86%) as a tan solid that was recrystallized from ethyl acetate−hexane to give colorless crystals: mp 100−101 °C, lit.[8] mp 100−101 °C; $[\alpha]^{23}_{D}$ +4.8° (*c* 1.03, $CHCl_3$), lit.[8] $[\alpha]^{25}_{D}$ +2.0° (*c* 3.7, $CHCl_3$); EIMS *m*/*z* 155 (M^+), 140, 126, 70, 59, 28; IR (KBr, cm^{-1}) ν_{max} 3418, 2972, 2888, 1659, 1458, 1366, 1082; ^{1}H NMR (300 MHz, $CHCl_3$) δ 3.67 (2H, m), 3.56 (1H, dt, J = 11.1, 7.5 Hz), 3.06 (1H, m), 2.73 (1H, m), 2.34 (1H, bs, disappeared with D_2O), 2.17 (1H, m), 2.01 (2H, m), 1.50 (1H, m), 1.21 (3H, d, J = 7.2 Hz).

Acknowledgment. We are pleased to thank the following for very necessary financial support: Outstanding Investigator Grant CA44344-05-12 awarded by the Division of Cancer Treatment and Diagnosis, National Cancer Institute DHHS; the Arizona Disease Control Research Commission; the Fannie E. Rippel Foundation; the Robert B. Dalton Endowment Fund; Gary L. and Diane Tooker; Polly J. Trautman; Billie Jean Baguley; Lottie Flugal; Dr. John C. Budzinski, and the Eagles Art Ehrmann Cancer Fund. For other helpful assistance, we thank Dr. Fiona Hogan.

JO010530T