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Stereoselective Synthesis of *iso*-Dolaproine via Dynamic Kinetic Resolution

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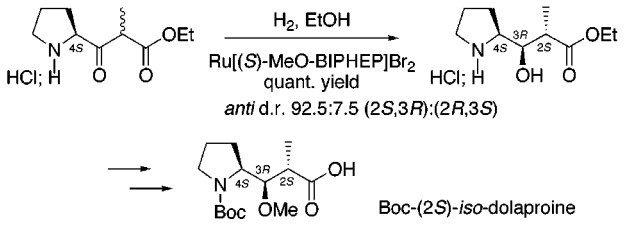
ABSTRACT



An efficient multigram-scale synthesis of optically pure Boc-(2*S*,3*R*,4*S*)-*iso*-dolaproine is reported using dynamic kinetic resolution (DKR). The catalytic asymmetric hydrogenation of ethyl (4*S*)-3-(2′-pyrrolidinyl)-3-oxo-2-methyl propanoate hydrochloride using in situ generated Ru[(*S*)-MeO-BIPHEP]Br_2 catalyst affords the *anti* β-hydroxy α-methyl ester quantitatively. The two new stereogenic centers are simultaneously controlled with high diastereoselectivity.

Dolastatin 10 exhibits powerful antineoplastic activity and is currently under clinical investigation as a new anticancer agent (Figure 1). Isolated from the Indian Ocean sea hare *Dolabella auricularia* by Pettit and co-workers, its structure was determined in 1987,[1] and the absolute configuration of its nine asymmetric centers was ascertained by total synthesis in 1989.[2a] Because of the limited amount of amorphous material available via extraction, there was an urgent need for an efficient synthetic route to this original pentapeptide. Pettit's group and others described practical syntheses of the pseudopeptide units and their coupling to provide larger supplies of Dolastatin 10 for its biological evaluation.[2a−g]

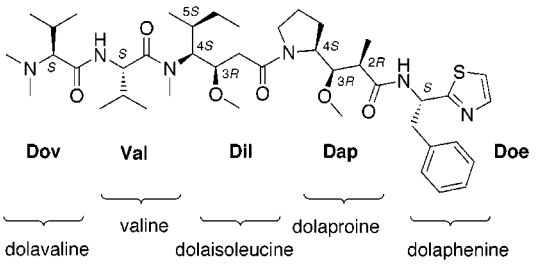


Figure 1. Dolastatin 10.

The linear structure of Dolastatin 10 (Figure 1) contains three unique units derived from α-amino acids: (*S*)-dolaphenine (Doe), (2*R*,3*R*,4*S*)-dolaproine (Dap), and (3*R*,4*S*,5*S*)-dolaisoleucine (Dil).

The most complex Dap unit contains three chiral centers and was the subject of many studies, mainly based on the

(1) Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tuinman, A. A.; Boettner, F. E.; Kizu, H.; Schmidt, J. M.; Baczynskyj, L.; Tomer, K. B.; Bontems, R. J. *J. Am. Chem. Soc.* **1987**, *109*, 6883.

(2) (a) Pettit, G. R.; Singh, S. B.; Hogan, F.; Lloyd-Williams, P.; Herald, D. L.; Burkett, D. D.; Clewlow, P. J. *J. Am. Chem. Soc.* **1989**, *111*, 5463. (b) Hamada, Y.; Hayashi, K.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 931. (c) Tomioka, K.; Kanai, M.; Koga, K. *Tetrahedron Lett.* **1991**, *32*, 2395. (d) Shioiri, T.; Hayashi, K.; Hamada, Y. *Tetrahedron* **1993**, *49*, 1913. (e) Roux, F.; Maugras, I.; Poncet, J.; Niel, G.; Jouin, P. *Tetrahedron* **1994**, *50*, 5345. (f) Pettit, G. R.; Srirangam, J. K.; Singh, S. B.; Williams, M. D.; Herald, D. L.; Barkoczy, J.; Kantoci, D.; Hogan, F. *J. Chem. Soc., Perkin Trans. 1* **1996**, *8*, 859 and references therein. (g) Recent review: Shioiri, T.; Hamada, Y. *Synlett* **2001**, 184.

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aldol condensation of *N*-protected (*S*)-prolinal with various propionyl enolates.

The best results were obtained by using a chiral oxazolidinone in the presence of dibutylboron triflate and triethylamine,[2b,d,3] giving exclusively the desired *syn* adduct. In contrast, the earlier use of a bulky chiral ester in the presence of magnesium bromide led to the *anti* adduct with moderate selectivity.[4] An achiral *Z*-boron enolate of thiophenyl propionate[2c] or an achiral *Z*-crotylboronate[2e] afforded the desired Dap unit after subsequent transformation but in lower yields, whereas the use of the simple benzyl propionate gave a *syn*/*anti* mixture in very low yield.[5]

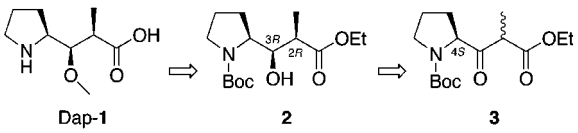
The need for larger amounts of Dolastatin 10 and analogues, stemmed by the increasing number of clinical trials in advanced phase, prompted us to explore a catalytic approach to Dolaproine avoiding the costly use of a stoichiometric amount of chiral auxiliary and the somewhat difficult preparation of (*S*)-prolinal.

In our continuous interest in ruthenium-catalyzed asymmetric hydrogenation,[6] we have already described several applications of this technology[7] to the synthesis of biologically or industrially relevant molecules.[8] On the basis of previous work on the asymmetric hydrogenation of chiral γ-amino β-keto esters,[9] we decided to investigate the reduction of γ-amino β-keto α-methyl esters derived from (*S*)-proline. The asymmetric hydrogenation of an α-substituted β-keto ester bearing a configurationally labile stereogenic center with chiral Ru(II) catalysts is known to give preferentially one of the four possible diastereoisomers via a dynamic kinetic resolution (DKR),[10] when optimum reaction conditions are used.

The selectivity of the dynamic kinetic resolution of α-substituted β-keto esters had already been studied in our group, showing a great dependence upon the reaction conditions and the substrate. Hydrogenation of α-acetamido β-keto esters[11] gave the *syn* adducts, whereas cyclic α-alkyl β-keto esters led to the *anti* β-hydroxy esters.,[1210a,b] We had also demonstrated that racemic α-chloro β-keto esters could be reduced to the desired *syn* or *anti* diastereoisomers with good to excellent de, depending on the choice of the solvent.[13] For racemic β-keto α-methyl esters, only three asymmetric reductions were reported, leading to 1:1 or 1:2 mixtures of *syn* and *anti* adducts in the case of methyl 2-methyl-3-oxobutanoate[14] or to a 7:1 mixture of *syn* and *anti* diastereoisomers in the case of methyl 2,4-dimethyl-3-oxopentanoate.[15] To the best of our knowledge, the asymmetric Ru(II)-catalyzed hydrogenation of α-substituted β-keto esters bearing an asymmetric center in the γ-position had not been reported. Therefore, we could hope that the outcome of the dynamic kinetic resolution would be in favor of the *syn* adduct in alcoholic solvents, as requested for the Dolaproine unit.

The retrosynthetic plan (Scheme 1) for Dolaproine was designed as follows: Dap-**1** would be obtained from the

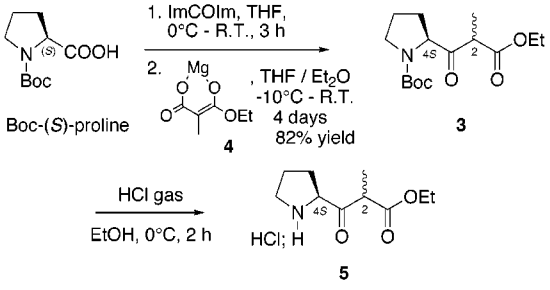
Scheme 1. Retrosynthetic Approach of Dolaproine-**1**



corresponding *N*-protected hydroxy ester **2** after methylation and saponification; the *syn* (*R*,*R*)-β-hydroxy α-methyl ester **2** would be preferentially produced by the Ru(II)-catalyzed hydrogenation of the corresponding β-keto α-methyl ester **3** using the atropoisomeric (*S*)-MeO-BIPHEP as a ligand.[16]

Synthesis of the hydrogenation substrate **3** (Scheme 2) from Boc-(*S*)-proline, carbonyldiimidazole (ImCOIm), and

Scheme 2. Synthesis of the Hydrogenation Substrate **5**



the magnesium enolate of ethyl hydrogen methylmalonate **4**[17] proceeded smoothly in 82% yield.

Early attempts to hydrogenate the *N*-Boc-protected γ-amino β-keto ester **3** proved to be difficult, in large part as a

(3) (a) Hayashi, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1991**, *32*, 7287. (b) Pettit, G. R.; Burkett, D. D.; Barkoczy, J.; Breneman, G. L.; Pettit, W. E. *Synthesis* **1996**, 719.

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

(5) Miyazaki, K.; Kobayashi, M.; Natsume, T.; Gondo, M.; Mikami, T.; Sakakibara, K.; Tsukagoshi, S. *Chem. Pharm. Bull.* **1985**, *43*, 1706.

(6) Reviews: (a) Genet, J.-P. In *Reductions in Organic Synthesis*; Magid, A., Ed.; ACS Symposium Series 641; American Chemical Society: Washington, DC, 1996; p 31. (b) Genet, J.-P. In *Advances in Asymmetric Synthesis*; Stephenson, G. R., Ed.; Chapman and Hall: London, 1996; p 60. (c) Ratovelomanana-Vidal, V.; Genet, J.-P. *J. Organomet. Chem.* **1998**, *567*, 163.

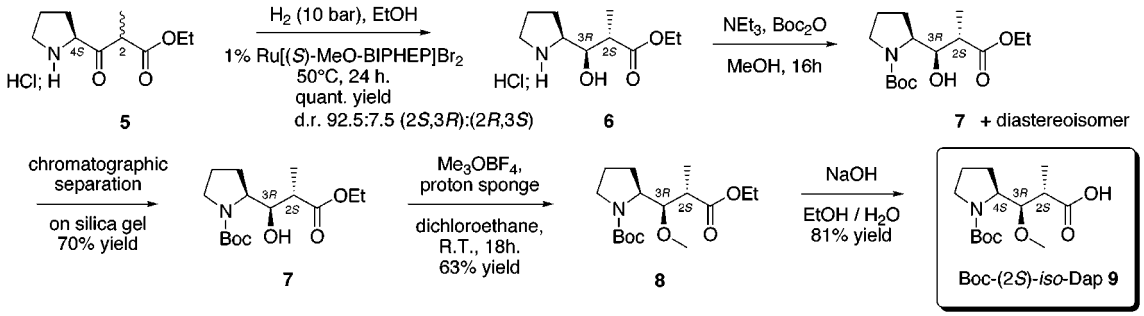
(7) (a) Marinetti, A.; Genet, J.-P.; Jus, S.; Blanc, D.; Ratovelomanana-Vidal, V. *Chem. Eur. J.* **1999**, *5*, 1160. (b) Blanc, D.; Ratovelomanana-Vidal, V.; Gillet, J.-P.; Genet, J.-P. *J. Organomet. Chem.* **2000**, *603*, 128. (c) Duprat de Paule, S.; Piombo, L.; Ratovelomanana-Vidal, V.; Greck, C.; Genet, J.-P. *Eur. J. Org. Chem.* **2000**, 1535. (d) Goulioukina, N. S.; Dolgina, T. M.; Beletskaya, I. P.; Henry, J.-C.; Lavergne, D.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Tetrahedron: Asymmetry* **2001**, *12*, 319.

(8) (a) Poupardin, O.; Greck, C.; Genet, J.-P. *Tetrahedron Lett.* **2000**, *41*, 8795. (b) Dolls, D. A.; Vanhessche, K. P. M.; Brazi, E.; Rautenstrauch, V.; Lenoir, J.-Y.; Genet, J.-P.; Wiles, J.; Bergens, S. H. *Angew. Chem., Int. Ed.* **2000**, *39*, 1992.

(9) (a) Nishi, T.; Kitamura, M.; Ohkuma, T.; Noyori, R. *Tetrahedron Lett.* **1988**, *29*, 6327. (b) Armstrong, J. D., III; Keller, J. L.; Lynch, J.; Liu, T.; Hartner, F. W. Jr.; Ohtake, N.; Okada, S.; Imai, Y.; Okamoto, O.; Ushijima, R.; Nakagawa, S.; Volante, R. P. *Tetrahedron Lett.* **1997**, *38*, 3203. (c) Ohtake, N.; Jona, H.; Okada, S.; Okamoto, O.; Imai, Y.; Ushijima, R.; Nakagawa, S. *Tetrahedron: Asymmetry* **1997**, *8*, 2939. (d) Guerreiro, P.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Chirality* **2000**, *12*, 408.

(10) (a) Noyori, R.; Ikeda, T.; Ohkuma, T.; Widhalm, M.; Kitamura, M.; Takaya, H.; Akutagawa, S.; Sayo, N.; Saito, T.; Taketomi, T.; Kumobayashi, H. *J. Am. Chem. Soc.* **1989**, *111*, 9134. Reviews: (b) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36. (c) Ratovelomanana-Vidal, V.; Genet, J.-P. *Can. J. Chem.* **2000**, *78*, 846.

Scheme 3. Dynamic Kinetic Resolution of **5** and Synthesis of Boc-(2*S*)-*iso*-Dap **9**



result of the very low conversion observed, even at high hydrogen pressure and temperature. However, after removal of the bulky *N*-Boc protecting group, the *N*-H;HCl γ-amino β-keto α-methyl ester hydrochloride **5** was found extremely reactive under moderate hydrogen pressure.[18]

The amine hydrochloride **5** was prepared from the corresponding *N*-Boc **3** in a single step by treatment with gaseous HCl in ethanol at 0 °C for 2 h (Scheme 2). The *tert*-butoxycarbonyl group was readily cleaved under these acidic conditions, and the resulting amine was converted into its hydrochloride salt. No workup was necessary, and simple evaporation of the solvent afforded the desired substrate **5** as a pink hygroscopic solid. ^{1}H NMR analysis of **5** in D_2O showed an equimolar mixture of 2*R* and 2*S* epimers.[19]

Hydrogenation of **5** was conducted with the simple in situ generated chiral ruthenium(II) catalysts[20] bearing atropoisomeric ligand (*S*)-MeO-BIPHEP (Scheme 3). The reaction conditions (1% cat., 10 bar, 50 °C, 24 h) and the choice of the configuration of the ligand were inspired by the results previously obtained with the analogous γ-amino β-keto ester derived from (*S*)-proline.[9d]

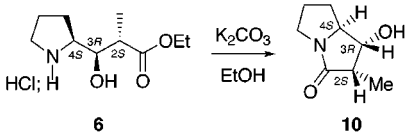
Analysis of the crude hydrogenation product **6** by ^{1}H NMR in D_2O allowed the determination of the conversion rate and stereoselectivity. Quantitative hydrogenation was observed, thus confirming the great influence of the unprotected γ-amino moiety in the conversion. Using racemic catalyst Ru[(±)-MeO-BIPHEP]Br_2, we observed a 46:54 mixture of *anti* (2*S*,3*R*)-**6** and *anti* (2*R*,3*S*) diastereoisomer, showing that the catalyst control is preferred over the substrate control.

The reaction using Ru[(*S*)-MeO-BIPHEP]Br_2 catalyst proceeded with excellent stereoselectivity, and the major diastereoisomer (2*S*,3*R*)-**6** was detected in a 92.5:7.5 ratio. This reaction can be conducted on a large scale, and we have routinely prepared batches of several grams of compound **6**.

To further confirm the composition of the hydrogenation product, the hydrochloride **6** was treated with Boc_2O and triethylamine to provide **7**. The GC analysis of this crude *N*-Boc product **7** on a chiral column (Lipodex A, isotherm 140 °C) confirmed that one compound largely dominated over some minor impurities. Silica gel flash chromatography was used to purify **7** in 70% yield with good chemical purity and excellent optical purity. At this stage, we had no information on the configuration of the major hydrochloride **6**.

The stereochemical assignment of **6** was firmly established by converting the crude hydrogenation product into the known[21] bicyclic lactam **10** (Scheme 4), whose characteristics

Scheme 4. Elucidation of the Configuration of **6**



(^{1}H NMR and $[\alpha]^{21}_D$ −109.3 (*c* 0.95, $CHCl_3$)) were consistent with literature data ($[\alpha]^{23}_D$ −97.9 (*c* 0.51, $CHCl_3$)[2d] and $[\alpha]^{30}_D$ −115 (*c* 1.85, $CHCl_3$)[2a,4] for (2*S*,3*R*)-**10**, different from $[\alpha]^{23}_D$ +4.53 (*c* 0.48, $CHCl_3$)[2d] for the (2*R*,3*R*)-bicyclic lactam). To our surprise, the dynamic kinetic resolution had generated almost exclusively the *anti*-**6** adduct, with excellent

(11) (a) Genet, J.-P.; Mallart, S.; Juge, S. French Patent 8911159, 1989. (b) Genet, J.-P.; Pinel, C.; Mallart, S.; Juge, S.; Thorimbert, S.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1991**, *2*, 555. (c) Girard, A.; Greck, C.; Ferroud, D.; Genet, J.-P. *Tetrahedron Lett.* **1996**, *37*, 7967. (d) Coulon, E.; Cano de Andrade, M. C.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Tetrahedron Lett.* **1998**, *39*, 6467. (e) Phansavath, P.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Eur. J. Org. Chem.* **2000**, 3903.

(12) Genet, J.-P.; Pfister, X.; Ratovelomanana-Vidal, V.; Pinel, C.; Laffitte, J. A. *Tetrahedron Lett.* **1994**, *35*, 4559.

(13) Genet, J.-P.; Cano de Andrade, M. C.; Ratovelomanana-Vidal, V. *Tetrahedron Lett.* **1995**, *36*, 2063.

(14) (a) Noyori, R.; Ohkuma, T.; Kitamura, M.; Takaya, H.; Sayo, N.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1987**, *109*, 5856. (b) Kitamura, M.; Ohkuma, T.; Tokunaga, M.; Noyori, R. *Tetrahedron: Asymmetry* **1990**, *1*, 1.

(15) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 1753.

(16) The choice of the configuration of the ligand follows the general rule for this reaction. For matched and mismatched pairs, see ref 9d.

(17) Matsubara, J.; Nakao, K.; Hamada, Y.; Shioiri, T. *Tetrahedron Lett.* **1992**, *33*, 4187.

(18) Similar change of reactivity had been described for functionalized γ-amino compounds; see ref 9c.

(19) The H−D exchange in the C2-position is so fast that no signal was observed for this proton. Such rapid α-equilibrium, associated with the good chiral recognition ability of the Ru-complex, should allow an efficient dynamic kinetic resolution process.

(20) Genet, J.-P.; Pinel, C.; Ratovelomanana-Vidal, V.; Mallart, S.; Pfister, X.; Cano de Andrade, M. C.; Laffitte, J. A. *Tetrahedron: Asymmetry* **1994**, *5*, 665.

(21) It has been established that *syn* (2*S*,3*R*) and *anti* (2*R*,3*R*) trifluoroacetate salts of **7** led without epimerization to (2*S*,3*R*)-**10** and (2*R*,3*R*) bicyclic lactams respectively (see ref 2a,d).

stereoselectivity. Up to now, we have no rational explanation for such an *anti* preference.

The synthesis of Boc-(2*S*)-*iso*-Dap **9** was achieved in two subsequent steps (Scheme 3). First, *O*-methylation of the hydroxy moiety with Me_3OBF_4 and proton sponge afforded the methoxy ester **8** in 63% yield. Then, saponification of the ethyl ester function with sodium hydroxide led to the *N*-Boc-protected (2*S*)-*iso*-Dolaproine **9** in 81% isolated yield as an off-white solid. Recrystallization from acetone/hexane afforded pure off-white crystals (rods) of **9** in 80% yield. Spectroscopical properties of this compound were identical with those described earlier.[4]

In summary, we have reported the first example of dynamic kinetic resolution of a γ-amino β-keto α-methyl ester as its hydrochloride salt via Ru(II)-catalyzed asymmetric hydrogenation. The *anti* β-hydroxy α-alkyl ester is almost exclusively produced because of the excellent discrimination of the chiral ruthenium(II) catalyst using (*S*)-MeO-BIPHEP. This technology opens access to efficient preparation of analogues of Dolaproine.

Acknowledgment. We thank Dr. R. Schmid (Hoffman−La-Roche) for samples of (*S*)-(−)-6,6′-dimethoxy-2,2′-bis-(diphenylphosphino)-1,1′-biphenyl (*S*)-MeO-BIPHEP). We are also very grateful to M.-N. Rager for help with the NMR analysis and to J. Marrache, who participated in the earlier studies of this work during his graduate project. Fellowships from C.N.R.S./D.G.A. (D.L.) and Ecole Polytechnique (C.M.) are gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterizations for new compounds **3** and **5**−**8** and for Boc-(2*S*)-*iso*-Dap **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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