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Kowalski Ester Homologation. Application to the Synthesis of β-Amino Esters

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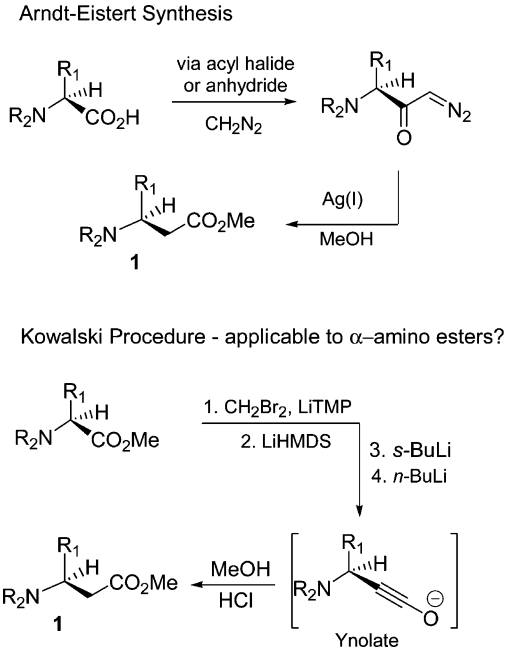
Abstract: The Kowalski ester homologation protocol has been applied to a representative range of α-amino esters to provide β-amino esters with excellent levels of enantio- and diastereocontrol. A key feature of this chemistry is the nature of the N-protecting group that is employed.

β-Amino acids represent an important class of biologically relevant molecules, being present within natural products and because of their use as key structural elements within medicinal chemistry.[1] More recently, β-amino acids have been utilized to produce unusual oligopeptide variants ("foldamers") that possess a range of interesting characteristics.[2] A number of methods are now available for the asymmetric synthesis of 2-substituted β-amino acids, which have been the subject of recent reviews.[3] The method of choice does, of course, depend on the specific target molecule, but the direct homologation of readily available and enantiomerically pure α-amino acids or esters provides a particularly attractive entry to their β-amino acid analogues, e.g., **1**.

Currently, homologations are based primarily on the Arndt−Eistert procedure, as outlined in Scheme 1. However this method, while widely used, necessarily requires the stoichiometric use of diazomethane and the generation and subsequent Ag(I)-catalyzed rearrangement of a diazoketone intermediate.[4] These are both significant drawbacks, especially for larger scale work, but a direct homologation strategy nevertheless retains significant advantages. Some years ago, Kowalski[5] reported a conceptually different approach to ester homologation involving an ynolate[6] as a key intermediate. This involves direct use of an ester substrate and avoids the need for both further activation and involvement of diazomethane and diazoketones. While the Kowalski protocol has been applied to a number of different substrates,[7] this chemistry had not been applied to the homologation of α-amino esters (see Scheme 1), and in this paper we outline our initial studies in this direction.

SCHEME 1. Arndt−Eistert vs Kowalski Protocols for the Homologation of α-Amino Acids or Esters



We had a particular requirement for enantiomerically pure homopipecolic acid, which has been prepared by the classical Arndt−Eistert sequence starting with pipecolic acid.[8] Initially two substrates were evaluated, the *N*-benzyl and *N*-Boc variants **2a**[9] and **2b**.[10] Under the Kowalski conditions, **2a** underwent smooth homologation, and after workup (MeOH, HCl) the corresponding ho-

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(1) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997. Bewley, C. A.; Faulkner, D. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2163-2178. Drey, C. N. C. In *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 25−54.

(2) Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219−3232. Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173−180. Seebach, D.; Matthews, J. L. *Chem. Commun.* **1997**, 2015−2022.

(3) Sewald, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 5794−5795. Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991−8035. Abele, S.; Seebach, D. *Eur. J. Org. Chem.* **2000**, 1−15. Juaristi, E.; Lopez-Ruiz, H. *Curr. Med. Chem.* **1999**, *6*, 983−1004. Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117−128. Cole, D. C. *Tetrahedron* **1994**, *50*, 9517−9582.

(4) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091−1160. Matthews, J. L.; Braun, C.; Guibourdenche, C.; Overhand, M.; Seebach, D. In *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp 105−126. Katritzky's benzotriazole-based homologation procedure, which also avoids use of diazomethane, has been compared directly to the Kowalski protocol (Katritzky, A. R.; Zhang, S.; Fang, Y. *Org. Lett.* **2000**, *2*, 3789−3791. Katritzky, A. R.; Zhang, S.; Hussein, A. H. M.; Fang, Y.; Steel, P. J. *J. Org. Chem.* **2001**, *66*, 5606−5612).

(5) Kowalski, C. J.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 7194−7208. Kowalski, C. J.; Lal, G. S. *Tetrahedron Lett.* **1987**, *28*, 2463−2466. Kowalski, C. J.; Lal, G. S. *J. Am. Chem. Soc.* **1986**, *108*, 5356−5357. Kowalski, C. J.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 1325−1327. Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, *108*, 7127−7128. Kowalski, C. J.; Haque, M. S.; Fields, K. W. *J. Am. Chem. Soc.* **1985**, *107*, 1429−1430. Kowalski, C. J.; Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140−5142.

(6) Shindo, M. *Synthesis* **2003**, 2275−2288. Shindo, M. *Chem. Soc. Rev.* **1998**, *27*, 367−374.

(7) For other examples of the application of the Kowalski homologation procedure, see: Smith, A. B.; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925−5937. Smith, A. B.; Kozmin, S. A.; Paone, D. *J. Am. Chem. Soc.* **1999**, *121*, 7423−7424. Suau, R.; López-Romero, J. M.; Rico, R.; Alonso, F. J.; Lobo, C. *Tetrahedron* **1996**, *52*, 11307−11320. Ballini, R.; Marcantoni, E.; Petrini, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 490−491.

(8) DeVita, R. J.; Goulet, M. T.; Wyvratt, M. J.; Fisher, M. H.; Lo, J. L.; Yang, Y. T.; Cheng, K.; Smith, R. G. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2621−2624. The Arndt−Eistert homologation of *N*-Boc-pipecolic acid was carried out via a mixed anhydride but no yields were reported.

(9) Quirante, J.; Escolano, C.; Bonjoch, J. *Synlett* **1997**, 179−180.

(10) Davies, C. E.; Heightman, T. D.; Hermitage, S. A.; Moloney, M. G. *Synth. Commun.* **1996**, *26*, 687−696.

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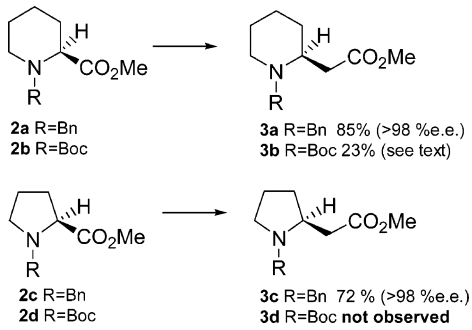
SCHEME 2. Kowalski Homologation of Pipecolic- and Proline-Derived Esters

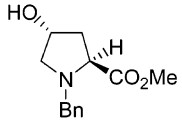
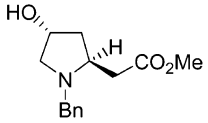
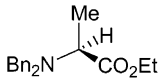
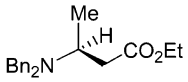
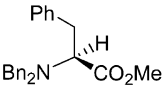
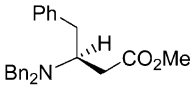
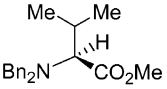
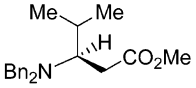


mologated ester **3a**[11] was isolated in 85% yield. Subjecting the *N*-Boc derivative **2b** to the same conditions gave the desired ester **3b**[12] but in only 23% isolated yield (Scheme 2).[13,14] The effect of the N-substituent is noteworthy, which also applied (and to a more significant extent) to the corresponding proline variants. Homologation of **2c**[15] gave the homoproline ester **3c**[16] in 72% yield, but when we attempted to use the *N*-Boc derivative **2d**, no homologated product **3d** was detected, although **2d** was consumed.

Crucial to the broader synthetic application of this methodology was the level of enantiomeric integrity associated with the homologated products. Using chiral HPLC, and with the corresponding racemate serving as the standard, the enantiomeric purity of **3a** was determined as being >98% ee; we were unable to detect any significant degree of racemization using the Kowalski procedure. Similarly, the proline derivative **2c** also underwent homologation to give **3c** in >98% ee.[17,18]

Given these observations, and the preference for *N*-benzyl over *N*-Boc, we examined a range of other readily available *N*-benzyl- or *N*,*N*-dibenzylamino esters as substrates for the Kowalski homologation procedure, the results of which are shown in Table 1. Methyl 4-hydroxyprolinate **2e**[19] underwent smooth homologation to provide

TABLE 1. Other Representative α-Amino Ester Homolgations

α-Amino Ester	β-Amino Ester yield; % d.e./e.e.
 **2e**	 **3e** 57 %; >98 %d.e.
 **2f**	 **3f** 52 %; >98 %e.e.
 **2g**	 **3g** 65 %; >98 %e.e.
 **2h**	 **3h** 10 %; %e.e. nd

3e as a single diastereomer in 57% yield.[20] This reaction proceeded *without the requirement to protect the secondary hydroxyl group*, which would be difficult to achieve under Arndt−Eistert conditions. Acyclic amino esters **2f**[21] and **2g**[22] also reacted well to provide the corresponding *β*-amino esters **3f**[23] and **3g**[24] in good yield with complete retention of stereochemistry.[25] In the case of **2f**, the ethyl ester was employed and the final quench was carried out with acidic ethanol to provide the homologated ethyl ester **3f**. The valine-derived ester **2h**[26] performed less efficiently. The yield of the homologated product **3h**[27] was poor (10%), and the enantiomeric purity of **3h** was not determined.

In summary, the Kowalski homologation protocol provides a viable and complementary alternative to the

(11) Racemic **3a** has been reported. Deutsch, H. M.; Dunn, T.; Ye, X. C.; Schweri, M. M. *Med. Chem. Res.* **1999**, *9*, 213−222.

(12) Morley, C.; Knight, D. W.; Share, A. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2903−2907.

(13) Given the widespread and popular use of *N*-Boc amino acids, it is appropriate to note that *N*-benzyl ester **3a** has been converted in essentially quantitative yield to the corresponding *N*-Boc derivative **3b** under standard conditions (H_2, 10% Pd/C, Boc_2O, MeOH, overnight). However, the optical rotation of **3b** ($[\alpha]^{22}_D = -18.0$ (*c* 4.45, $CHCl_3$)) differed from that described earlier which was reported as $[\alpha]_D = -8.3$ (*c* 4.54, $CHCl_3$).[12] On the basis of a reexamination of the original experimental data, it is clear that this discrepancy is due to a error in the earlier paper which should read as $[\alpha]_D = -18.3$ (*c* 4.54, $CHCl_3$) (Knight, D. W. Personal communication).

(14) Reactions of **2a** and **2b** were initially conducted using the more available racemic pipecolinic acid derivatives, and because of the low yield of **3b** obtained from **2b** this reaction was not carried out with enantiomerically pure material. *N*-Boc (*S*)-**3b** is, however, readily prepared.[13]

(15) Corey, E. J.; Link, J. O. *J. Org. Chem.* **1991**, *56*, 442−444.

(16) Govindachari, T. R.; Rajagopalan, T. G.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1161−1165.

(17) Optical rotation data for (*S*)-**3c**: $[\alpha]^{23}_D = -68.2$ (*c* 2.1, $CHCl_3$) [lit.[16] for (*S*)-**3c** $[\alpha]^{25}_D = -67.8$ (*c* 2, $CHCl_3$)].

(18) Chiral HPLC employed a Chiralcel OD column, eluting with hexane−propan-2-ol (98:2). The homologation of **2c** was carried out successfully (72% yield) on a 23 mmol scale (5 g of **2c**).

(19) Rosen, T.; Chu, D. T. W.; Lico, I. M.; Fernandes, P. B.; Marsh, K.; Shen, L.; Cepa, V. G.; Pernet, A. G. *J. Med. Chem.* **1988**, *31*, 1598−1611.

(20) *O*-TBS-protected methyl 4-hydroxyprolinate gave the corresponding homologated product in a modest 25% yield but with no loss of diastereomeric integrity. ^{1}H NMR spectra for both *O*-TBS-protected methyl 4-hydroxyprolinate and the corresponding homologated product are also available in the Supporting Information.

(21) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696−6699.

(22) Hoffman, R. V.; Tao, J. H. *J. Org. Chem.* **1997**, *62*, 2292−2297.

(23) Décombe, J. *Ann. Chim.* **1932**, *18*, 81−187. The corresponding methyl ester has also been described; see: Asao, N.; Uyehara, T.; Yamamoto, Y. *Tetrahedron*, **1988**, *44*, 4173−4180.

(24) Gmeiner, P.; Hummel, E. *Synthesis* **1994**, *10*, 1026−1028.

(25) Small amounts of the corresponding α-bromo ketones, resulting from quenching of the initial $LiCHBr_2$ adduct to the α-amino ester, were also isolated. See: Barluenga, J.; Baragaña, B.; Concellón, J. M.; Pinera-Nicolás, A.; Díaz, M. R.; García-Granda, S. *J. Org. Chem.* **1999**, *64*, 5048−5052.

(26) Davidsen, S. K.; Chumoyer, M. Y. *J. Org. Chem.* **1989**, *54*, 5558−5567.

(27) Tussa, L.; Lebreton, C.; Mosset, P. *Chem. Eur. J.* **1997**, *3*, 1064−1070.

Arndt−Eistert procedure for the synthesis of enantiomerically pure β-amino esters. This chemistry, though it looks operationally complicated, is quite straightforward and is all carried out in a one-pot procedure. Since the Kowalski protocol avoids the need to handle potentially hazardous intermediates, such as diazomethane and diazoketones, this becomes attractive for larger scale work. Further work is underway to extend the scope of this chemistry, given the obvious advantages associated with the ability to apply this procedure to carbamate-protected amino esters. These results will be reported in due course.

Experimental Section[28]

Methyl (*S*)-*N*-Benzylpiperidin-2-ylacetate 3a. A solution of LTMP was prepared as follows: A solution of *n*-BuLi in hexanes (1.1 mL, 3.1 mmol) was added to a stirred, cold (0 °C) solution of TMP (0.6 mL, 3.3 mmol) in THF (4.3 mL). In a separate flask, a stirred mixture of methyl (*S*)-*N*-benzylpipecolinate **2a** (216 mg, 0.9 mmol) and CH_2Br_2 (0.2 mL, 3.1 mmol) in THF (4.3 mL) was cooled to −78 °C. After 30 min, the LTMP solution was cooled to −78 °C and added to the **2a**/CH_2Br_2 mixture dropwise via a double-ended needle, and after 15 min, a cold (−78 °C) solution of LHMDS in THF (2.8 mL, 3.1 mmol) was added dropwise via a double-ended needle. The mixture was then allowed to warm to −20 °C and was then recooled to −78 °C, and a solution of *s*-BuLi in hexanes (3.6 mL, 4.7 mmol) was added dropwise. The mixture was then warmed to −20 °C, and a solution of *n*-BuLi in hexanes (1.1 mL, 2.8 mmol) was added. The mixture was warmed to rt, stirred for 1 h, and then quenched over a 20 min period into a stirred solution of acidic methanol (12 mL) at 0 °C. (Acidic methanol was prepared by slow addition of acetyl chloride to ice-cooled dry methanol (1:5 ratio/vol)). The mixture was diluted with ether (150 mL) and washed with $NaHCO_3$ (sat.). The aqueous phase was reextracted with ether (2 × 50 mL), and the combined organic extracts were washed with brine, dried (Mg_2SO_4), and concentrated in vacuo, and purification by flash chromatography (hexane/EtOAc, 9/1−3/2) gave ester **3a** (195 mg, 85%): R_f 0.55 (hexane/EtOAc1/1); $[\alpha]^{23}_D = -50$ (*c* 1.6, $CHCl_3$); IR (neat) 1734, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21−1.79 (6H, m, H-3, H-4, H-5), 2.18 (1H, m, H-2), 2.47 (1H, dd, J = 14.6, 7.7 Hz, CH_2CO), 2.63 (1H, m), 2.71 (1H, dd, J = 14.6, 4.8 Hz, CH_2CO), 2.97 (1H, m, H-6), 3.35 (1H, d, J = 13.2 Hz, benzylic), 3.73 (3H, s, OCH_3), 3.78 (1H, d, J = 13.2, benzylic), 7.26−7.32 (5H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 22.4 (C-4), 25.2 (C-3), 30.9 (C-5), 36.1 (CH_2CO), 50.2 (C-6), 51.5 (OCH_3), 57.6 (benzylic), 58.6 (C-2), 126.8, 128.2, 128.8 and 139.6 (aromatic), 173.2 (CO); MS (CI) *m*/*z* 248 (100, MH^+); HRMS (CI^+) calcd for $C_{15}H_{22}NO_2$ (MH^+) 248.1651, found 248.1652.

Chiral HPLC was carried out using a Chiralcel OD column, using hexane/propan-2-ol (98:2) at 1 $mLmin^{-1}$. Under these conditions, (*S*)-**3a** had a retention time of 17.03 min and (*R*)-**3a** had a retention time of 19.01 min. (*S*)-**3a** was correlated to (*S*)-**3b**, which has already been described in the literature.[13]

Methyl (2*S*,4*R*)-(*N*-Benzyl-4-hydroxypyrrolidin-2-yl)acetate 3e. A solution of LTMP was prepared as follows: A solution of *n*-BuLi in hexanes (3.9 mL, 9.4 mmol) was added to a stirred, cold (0 °C) solution of TMP (1.8 mL, 10.2 mmol) in THF (9 mL). In a separate flask, a stirred mixture of (2*S*,4*R*)-*N*-benzyl-4-hydroxy-L-proline methyl ester **2e** (500 mg, 2.1 mmol) and CH_2Br_2 (0.7 mL, 9.4 mmol) in THF (9 mL) was cooled to −78 °C. After 30 min, the LTMP was cooled to −78 °C and added to the **2e**/CH_2Br_2 mixture dropwise via a double-ended needle, and after 15 min, a −78 °C solution of LHMDS in THF (8.6 mL, 8.5 mmol) was added dropwise via a double-ended needle. Following the addition, the mixture was allowed to warm to −20 °C and was then recooled to −78 °C, and a solution of *s*-BuLi in hexanes (14.2 mL, 8.5 mmol) was added dropwise. The mixture was then warmed to −20 °C, and a solution of *n*-BuLi in hexanes (3.5 mL, 8.5 mmol) was added. The mixture was warmed to rt, stirred for 1 h, and then quenched over a 20 min period into a stirred solution of acidic methanol (see above) (18 mL) at 0 °C. The mixture was diluted with ether (250 mL) and washed with $NaHCO_3$ (sat.). The aqueous phase was reextracted with ether (2 × 100 mL), and the combined extracts were washed with brine, dried (Mg_2SO_4), and concentrated in vacuo, and purification by flash chromatography (EtOAc) gave **3e** (298 mg, 57%): R_f 0.33 (EtOAc); $[\alpha]^{23}_D = -182$ (*c* 2.87, $CHCl_3$); IR (neat) 3398, 1734, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.86−2.00 (2H, m, CH_2CO), 2.19−2.23 (1H, q, J = 4.0 Hz, H-3), 2.31−2.37 (1H, q, J = 8.0 Hz, H-3), 2.64−2.68 (1H, br, OH), 2.69−2.64 (1H, dd, J = 16.0, 4.0 Hz, H-5), 3.14−3.19 (2H, m, H-4, H-5), 3.34−3.36 (1H, J = 12.0 Hz, benzylic), 3.65 (3H, s, OCH_3), 3.94−3.98 (1H, d, J = 12.0 Hz, benzylic), 4.26−4.31 (1H, m, H-2), 7.23−7.32 (5H, m, aromatic); ^{13}C NMR ($CDCl_3$) δ 39.0 (C-3), 41.5 (CH_2CO), 51.6 (OCH_3), 58.3 (C-5), 59.2 (C-2), 62.2 (benzylic), 69.5 (C-4), 127.1, 128.3, 128.5, 128.7, 128.8, and 139.1 (aromatic), 172.5 (CO); CIMS *m*/*z* 250 (75, MH^+); HRMS (CI^+) Calcd for $C_{14}H_{20}NO_3$ (MH^+) 250.1443, found 250.1438.

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Supporting Information Available: ^1H NMR spectra for starting amino esters and homologated products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) The homologation procedure described for the preparation of **3a** was used for all other cases reported in this paper, with the exception of **3e**; this latter case is also presented in the Experimental Section. All ^1H and ^{13}C NMR assignments are based on COSY methods.