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Total Synthesis of the Amaryllidaceae Alkaloid (+)-Plicamine and Its Unnatural Enantiomer by Using Solid-Supported Reagents and Scavengers in a Multistep Sequence of Reactions**

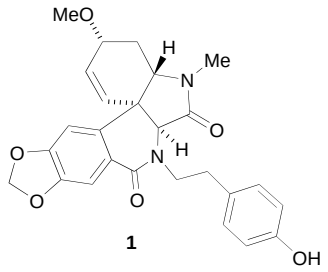
Ian R. Baxendale, Steven V. Ley,* and Claudia Piutti

Amaryllidaceae alkaloids are an important class of natural products especially as many members of the series display a wide range of potent biological activity. These properties include anticholinergic, antitumor, immunosuppresive, and analgesic activity, and they have also been shown to inhibit various cell cycle mechanisms (including HIV-1 activity), and have found recent application in the therapeutic treatment of Alzheimer's disease.[1] Thus extensive synthetic studies of this family have been carried out over a number of years.[2, 3] Furthermore, the search for new members of the series has proved to be extremely profitable.[3, 4] The recently isolated compound (+)-plicamine (**1**) is especially attractive as it exemplifies many of the structural features of these natural

[*] Prof. S. V. Ley, I. R. Baxendale
Department of Chemistry
University of Cambridge
Lensfield Road, Cambridge CB2 1EW (UK)
Fax: (+44) 1223-336-442
E-mail: svl1000@cam.ac.uk
C. Piutti
Department of Chemistry
Pharmacia S.p.A
Discovery Research Oncology
Viale Pasteur, 10, 20014 Nerviano (MI) (Italy)

[**] We gratefully acknowledge financial support from Pfizer Central Research for a Postdoctoral Fellowship (to I.R.B.), the BP endowment and the Novartis Research Fellowship (to S.V.L.), and Pharmacia & Upjohn (to C.P.).

  1433-7851/02/4112-2194 $ 20.00+.50/0



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products and has not been previously synthesized nor have its biological properties been fully evaluated.[5]

Here, we report a conceptionally interesting approach to both enantiomers of plicamine **1** using an orchestrated multistep sequence of reactions, for which only solid-supported reagents and scavengers are used to effect the individual steps.[6] In this way, work-up of the reaction mixture is greatly facilitated, requiring only the simple operation of filtration to remove spent or excess reagents followed by evaporation to afford the product. No conventional work-up procedures such as chromatography, crystallization, or distillation are necessary. These methods not only expediate the synthesis reported here but also have relevance for chemical compound library generation. For example, we have previously shown that these approaches can be used to prepare druglike substances,[7] heterocyclic compounds,[8] and other natural products.[9]

Both enantiomers of plicamine **1** have been synthesized by the appropriate selection of the commercially available optically pure form of 4-hydroxyphenylglycine. The synthesis of (+)-plicamine reported below, begins with the conversion of L-4-hydroxyphenylglycine to the amide **2** (see Scheme 1). The initial reaction with trimethylsilyl chloride (TMSCl) in methanol resulted in the formation of an intermediate methyl ester. Subsequent treatment with Amberlyst 21 resin, to act as a scavenger for hydrochloric acid, produced the free base. Addition of excess methylamine to the reaction mixture afforded the amide **2** in essentially quantitative yield. At all stages of the synthesis the product purity was evaluated by LC-MS and in all cases was found to be in excess of 95% unless stated. This level of purity was more than adequate to progress directly to the next step in the synthesis. Following procedures reported previously for the synthesis of oxomaritidine,[9c] the amino group in **2** was allowed to react with piperonal **3** and the resulting imine reduced with polymer-supported borohydride[10] in methanol and dichloromethane to give the reductively aminated product. The amine was immediately acylated with trifluoroacetic anhydride to give the protected amine **4**. Polymer-supported aminomethylpyridine (poly-DMAP) in the presence of polyvinylpyridine (PVP) was used as the catalyst in this transformation.[11] All these reactions were easily carried out on multigram scale to give the clean product **4** in 91% overall yield over the six steps (>97% purity by HPLC; Scheme 1). Phenol oxidative coupling of **4** gave the spirodieneone **5** (82% yield)[12] through the use of the solid-supported iodonium diacetate[13] in 2,2,2-trifluoroethanol as the solvent. Compound **5** was efficiently cyclized to the tetracyclic lactam **6** by using Nafion-H resin in dichloromethane (alternatively a solution of HCl in diethyl ether could be employed). Again the purity of the product at all stages of this synthesis was excellent, the product required no chromatography prior to advancing to the next step. The ketone **6** was stereoselectively reduced by using polymer-supported borohydride,[14] and the resulting alcohol was methylated by using trimethylsilyldiazomethane and a macroporous sulfonic acid exchange resin to give **7**.[15] The stereoselectivity in this reaction was confirmed by X-ray crystallographic studies and detailed NOE experiments. Next, the trifluoroacetate protecting group was removed by treatment with Ambersep 900 (OH^- form) in methanol in a sealed tube microwave reactor at 100 °C for 20 min.[16] The intermediate amino compound **8** was readily alkylated with bromide **10** in the presence of a solid-supported carbonate base[17] to give **9**. Excess bromide **10** was scavenged by using a mercaptoaminomethyl resin[18] and the product was obtained in excellent yield and purity. It should be noted that the bromide **10** is not commercially available and was prepared from the corresponding alcohol **11** by using carbon tetrabromide or bromine and an immobilized triphenylphosphane.[19] The alkylated material **9** was immediately oxidized to the amide **1** by using chromium trioxide and 3,5-dimethylpyrazole.[20] This reaction proved to be the most difficult transformation in the sequence, requiring scavenging with solid Amberlyst 15 resin to remove contaminating unoxidized amine and the pyrazole. The chromium salts could be efficiently removed by passing the reaction mixture through a mixed-bed column of Varian Chem Elut CE1005 packing material[21] and montmorillonite K 10 (1:1 wt/wt), which had been preconditioned by eluting with a 10:1 mixture of acetonitrile/water. After this process of scavenging, (+)-plicamine **1** was obtained in 70% yield and greater than 90% purity (by HPLC). To obtain analytically pure material a rapid pass through a short plug of silica gel was sufficient.[22] Following the same reaction sequence, we have also been able to prepare the unnatural enantiomer (−)-plicamine in essentially identical yields and purity starting from D-4-hydroxyphenylglycine.[23]

In summary, we have reported the first total synthesis of (+)-plicamine (**1**) and its enantiomer using only a combination of supported reagents and scavengers to effect all the synthetic steps. No less than thirteen immobilized systems were used to produce the clean product. Given the relative complexity of the molecule, the synthesis is a powerful demonstration of the ability to achieve multistep transformations without conventional chromatographic methods.

Received: February 15, 2002 [Z18719]

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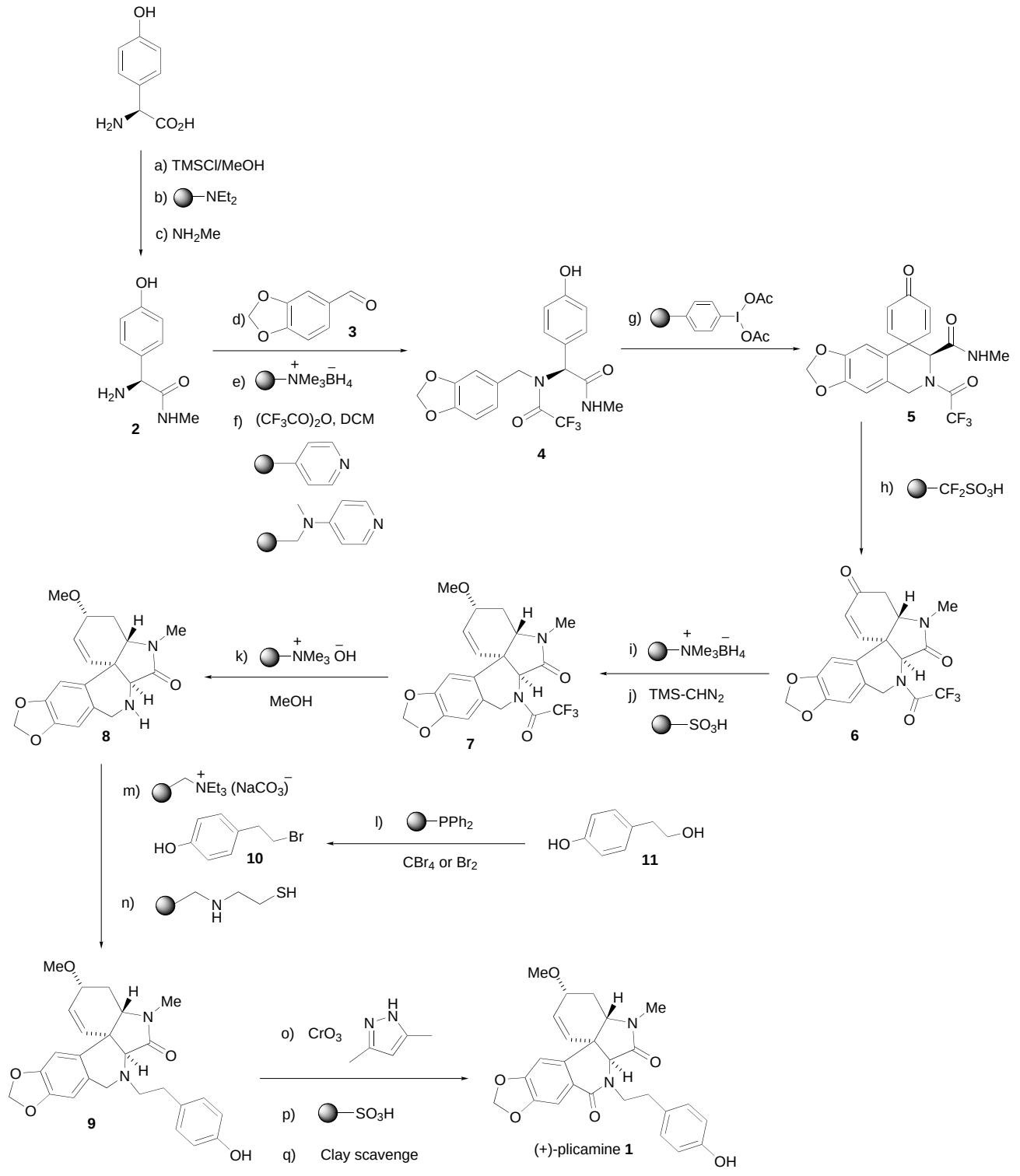

Scheme 1. Total synthesis of (+)-plicamine (**1**). a) TMSCl (3 equiv), MeOH, RT, 12 h; b) Amberlyst 21 (3 equiv ~3 mmol g^{-1}); c) NH_2Me (5 equiv), MeOH, 40 °C, 24–48 h; d) piperonal **3** (1.1 equiv), EtOAc, RT, 45 min; e) PS-borohydride, MeOH/CH_2Cl_2 (2:1), 2 h; f) $(CF_3CO)_2O$, PVP (3 equiv), poly-DMAP (0.5 equiv), CH_2Cl_2, 0 °C, 1 h, (91% over six steps); g) PS-iodinium diacetae (1.5 equiv), 2,2,2-trifluoroethanol, −5 °C, 82%; h) Nafion-H, 24 h; i) PS-borohydride, MeOH/CH_2Cl_2 (1:1) 2 h, quantitative; j) TMS-CHN_2, sulfonic acid resin, MeOH/CH_2Cl_2 (3:2), 95%; k) Ambersep 900 (OH^-), MeOH, microwave, 100 °C, 20 min, 96%; l) PS-triphenylphosphane (2 equiv), CBr_4 (1.5 equiv) or Br_2 (1.5 equiv), CH_2Cl_2, 0 °C, 1 h, quantitative; m) PS-carbonate (2 equiv), bromide **10** (1.2 equiv), MeCN, microwave, 140 °C, 2 × 15 min; n) PS-mercaptoaminomethyl resin, 90% (two steps); o) CrO_3 (2.5 equiv), 3,5-dimethylpyrazole (2.5 equiv), CH_2Cl_2, −45 °C, 4 h, 82% conversion by LC-MS; p) Amberlyst 15 (10 equiv); q) (1:1 wt/wt) montmorillonite K 10/Varian Chem Elut CE1005 packing material, 70% (isolation for three steps o–q).

  1433-7851/02/4112-2196 $ 20.00+.50/0 *Angew. Chem. Int. Ed.* **2002**, *41*, No. 12

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[11] Available from Aldrich, dimethylaminopyridine, polymer-bound (cat. no. 35,988-2); poly(4-vinylpyridine) 2 % cross-linked (cat. no. 22,696-3).

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[14] Borohydride on polymer support (Amberlyst A-26 BH_4^- form, 1.5 – 4 mmol g^{-1}) available from Fluka (cat. no. 15595). The use of immobilised borohydride on Amberlite IRA 400[10] resulted in significant amounts of deprotected amino alcohol material. As an alternative, polymer-supported cyanoborohydride could be used, but in this case the reactions required more than 48 h.

[15] MP-TsOH 1.40 mmol g^{-1} available from Argonaut Technologies Inc. (cat. no. 800286; A15 was not effective in promoting this transformation).

[16] A fully automated Coherent Synthesis System microwave machine was used. This was supplied by Personal Chemistry: Hamnesplanaden 5, 753 19 Uppsala, Sweden; www.personalchemistry.com.

[17] *N*-(2-mercaptoethyl)aminomethyl polystyrene 1.2 mmol g^{-1} available from Nova Biochem. (cat. no. 01-64-0180).

[18] Carbonate on polymer support on IRA 900, $\sim$3.5 mmol g^{-1} ($NaCO_3$) available from Fluka (cat. no. 21850).

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[21] Varian Chem. Elut Column (cat. no.1219-8007).

[22] (+)-Plicamine $[\alpha]_D = +77.5$ ($c = 0.867$ in MeOH); $[\alpha]_D^{lit} = +74.4$ ($c = 0.117$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.59$ (s, 1H; H-9), 7.08 (d, $J = 8.3$ Hz, 2H; H-2′ and H-6′), 6.73 (d, $J = 8.3$ Hz, 2H; H-3′ and H-5′), 6.49 (s, 1H; H-12), 6.01 (s, 2H; OCH_2O), 5.81 (d, $J = 10.1$ Hz, 1H; H-2), 5.36 (d, $J = 10.1$ Hz, 1H; H-1), 4.51 (ddd, $J = 13.8$, 8.3, 4.3 Hz, 1H; H-8′a), 4.06 (m, 1H; H-4a), 3.93 (s, 1H; H-6a), 3.87 (dd, $J = 12.3$, 4.3 Hz, 1H; H-4a), 3.51 (m, 1H; H-8′b), 3.44 (s, 3H; OMe), 2.93 (m, 2H; H-7′), 2.78 (s, 3H; NMe), 2.58 (m, 1H; H-3β), 1.39 ppm (m, 1H; H-3α); IR (neat): $\tilde{\nu}_{max} = 3292.7$, 2976.2, 2983.7, 1705.8, 1668.7, 1613.3, 1514.5, 1482.7, 1442.7, 1400.7, 1386.1, 1348.3, 1233.6, 1158.4, 1102.8, 1036.2, 931.9, 929.8 cm^{-1}; HR-MS calcd for $C_{26}H_{26}N_2O_6Na$: 485.1689; found 485.1694. Numbering from original paper concerning isolation see reference [5a].

[23] (−)-Plicamine $[\alpha]_D = -76.5$ ($c = 0.678$ in MeOH).

Catalytic Enantioselective Synthesis of β^2-Amino Acids**

Huw M. L. Davies* and Chandrasekar Venkataramani

In recent years the enantioselective synthesis of β-amino acids has been of considerable interest because β-amino acids[1] are useful precursors of β-peptides[2] and β-lactams.[2b, 3] Traditionally, the asymmetric synthesis of β^2-substituted amino acids has been achieved by using chiral auxiliaries in methods such as the alkylation of chiral enolates[4] and the acylation of metalated phenylacetonitrile with a chiral carbonyl chloride.[4c] Recently, highly enantioselective, L-proline-catalyzed, asymmetric Mannich-type reactions of *N*-PMP-protected (PMP = *p*-(MeO)C_6H_5) α-iminoethyl glyoxylate with aldehydes to generate functionalized β-amino acids was reported.[5] Herein we report a catalytic asymmetric synthesis of β^2-substituted amino acids. The crucial reaction is an asymmetric C–H activation of *N*-butoxycarbonyl (Boc)-protected methylamines by means of a [Rh_2(*S*-DOSP)$_4$] (**1**) induced C–H insertion [Eq. (1); TFA = trifluoroacetic acid].

Recently, numerous applications of the rhodium – carbenoid induced intermolecular C–H activation strategy in

[*] Prof. H. M. L. Davies, C. Venkataramani
Department of Chemistry, University at Buffalo
The State University of New York
Buffalo, NY 14260-3000 (USA)
Fax: (+1) 716-645-6547

[**] This work was supported by the National Science Foundation (CHE 0092490) and the National Institutes of Health (GM57425).

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