Stereoselective Synthesis of Arylglycine Derivatives using Arene–manganese Tricarbonyl Complexes

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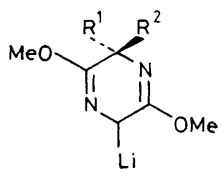
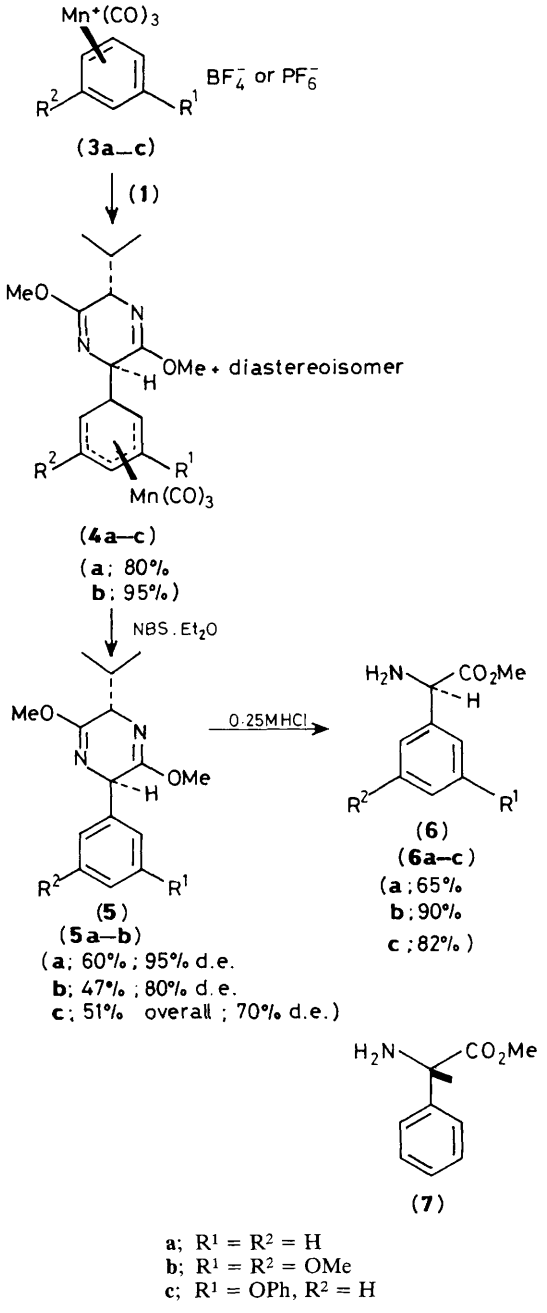
Arene–$Mn(CO)_3$ cations react with the Schöllkopf chiral glycine enolate equivalent (**1**) or (**2**) to give dienyl–$Mn(CO)_3$ complexes which are converted to arylglycine methyl esters; the reaction sequence can be performed on arene–$Mn(CO)_3$ complexes having protected amino acid substituents to give diaryl ethers having amino ester groups on both aromatic rings.

We recently described a method for *O*-phenylation of protected tyrosine and 4-hydroxyphenylglycine derivatives using a chlorobenzene–manganese tricarbonyl cation, which proceeded under very mild conditions and without detectable racemisation in the amino acid side chain.[1] If this chemistry can be developed to allow the construction of diaryl ethers having amino acid groups attached to *both* aromatic rings, it should provide access to subunits required for the synthesis of complex glycopeptide antibiotics such as vancomycin and ristocetin A,[2] as well as simpler peptides containing aryl ether linkages.[3] We report herein our preliminary studies on the conversion of arene–$Mn(CO)_3$ complexes to aryl glycines *via* their reaction with the Schöllkopf chiral glycine enolate equivalent[4] (**1**) or (**2**), which proceeds satisfactorily using arene–$Mn(CO)_3$ systems having protected amino acid moieties in the side chain.

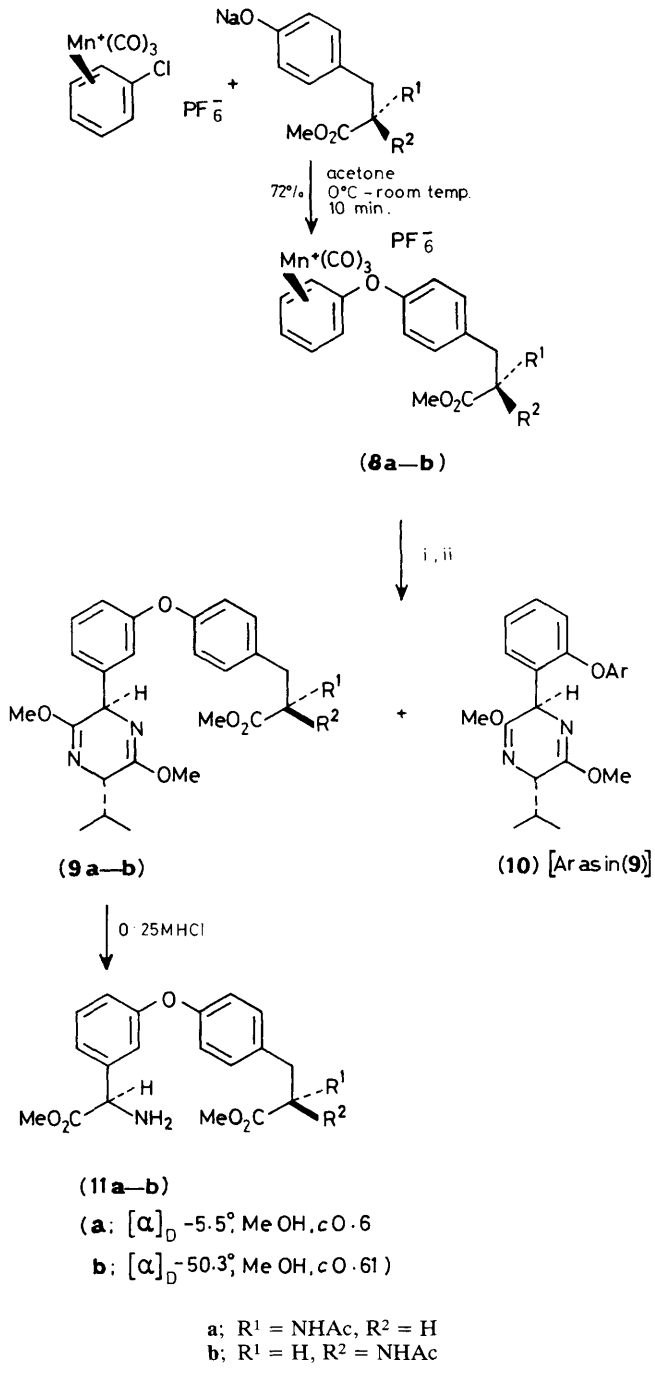
Initial experiments utilised the simple arene–$Mn(CO)_3$ complexes (**3**), which were treated with (**1**) [1 equiv.,



(**1**) $R^1 = Pr^i$, $R^2 = H$
(**2**) $R^1 = H$, $R^2 = Pr^i$



Scheme 1

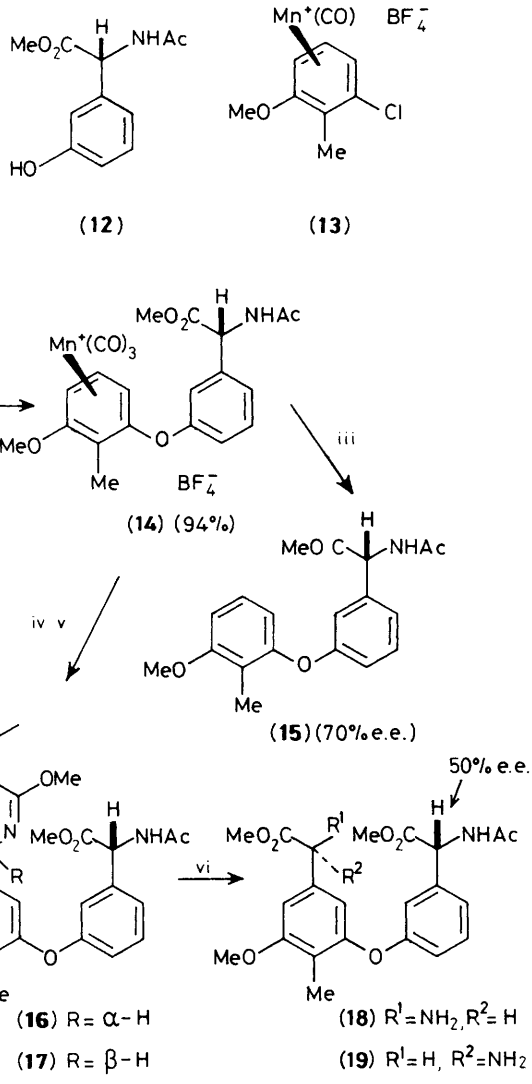


Scheme 2. *Reagents and conditions*: i, (**1**), −100 °C; ii, NBS, Et_2O.

tetrahydrofuran (THF), −78 °C, 30 min] to give the substituted cyclohexadienyl–$Mn(CO)_3$ complexes† (**4**) in good yield and high diastereoisomeric excess (d.e.) (Scheme 1). Treatment of these compounds with *N*-bromosuccinimide (1.0 equiv., Et_2O, room temp., 15 min) effected oxidative demetallation to give the aromatic compounds (**5**). Chromatographic separation of diastereoisomers, followed by hydrolysis of the dihydropyrazine (0.25 M HCl, room temp., 10 h, followed by pH adjustment to *ca.* 8 using aqueous ammonia), afforded the arylglycine methyl ester derivatives (**6**) in optically pure form [by n.m.r. in the presence of tris-(heptafluorobutyrylcamphorato)europium(III), Eu(hfbc)$_3$]. The absolute configuration of the products from this sequence was confirmed by converting (**2**) to (*S*)-phenylglycine methyl ester (**7**) ([α]$_D$ +130°, MeOH, *c* 0.02) and comparison with a sample prepared from commercially available (*S*)-phenylglycine.

In order to test the applicability of this method to the preparation of arylglycines of the type present in vancomycin and ristocetin A, we examined the reactions of complexes (**8a**) ([α]$_D$ +3.8°, MeCN, *c* 1.0) and (**8b**) ([α]$_D$ −4.3°, MeCN, *c*

† All new compounds were characterised using 200 MHz n.m.r., i.r., and high resolution mass spectrometry. The reaction of (**3c**) with (**1**) resulted in predominantly *meta* addition, but a minor amount of product from *ortho* attack was also formed (ratio 14 : 1). When two alkoxy substituents are present, as in (**3b**), a single product (**4b**) is given.

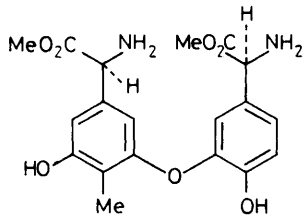


Scheme 3. *Reagents and conditions*: i, NaH, THF, −20 °C; ii, (**13**), $AgBF_4$, acetone, 0 °C; iii, MeCN; iv, THF, −78 °C; v, NBS, Et_2O, room temp.; vi, 0.25 M HCl.

1.0), both readily prepared by a slight modification of our previously published method[1] (Scheme 2). Treatment of (**8**) with nucleophile (**1**) at −78 °C gave none of the desired product; *O*-phenyl-*N*-acetyltyrosine methyl ester, resulting from loss of the $Mn(CO)_3$ group, was isolated instead. When this reaction was conducted at −100 °C, using 2 equiv. of (**1**) (time 2 h), a diastereoisomeric mixture of complexes resulted,‡ which was converted directly to the diaryl ether derivatives, obtained as a *ca.* 10:1 mixture of *meta*- and *ortho*-adducts (**9**) and (**10**) in 49% overall yield§ [64.70% d.e. for (**9**)]. Hydrolysis of (**9**) with 0.25 M HCl as above gave (**11**), but in rather disappointing yield (28—30%). N.m.r. spectroscopy in the presence of $Eu(hfbc)_3$, comparing (**11a**) with a mixture of (**11a**) and (**11b**), indicated that no racemisation of the tyrosine residue occurs throughout this sequence.

‡ Since the dienyl–$Mn(CO)_3$ system itself is a centre of asymmetry in compound (**4c**), and those resulting from nucleophile addition to (**8**) and (**14**), these give twice as many diastereoisomers, and were oxidized directly to the aryl ether derivatives without purification.

§ The ratio of 9:10 varied from 8:1 to 14:1.



Commercially available (*R*)-3-hydroxyphenylglycine was converted by standard methods to the *N*-acetyl methyl ester derivative (**12**) [obtained in 84% enantiomeric excess (e.e.)]. The manganese complex (**13**) was prepared in 94% yield from 3-chloro-2-methylanisole using a modification of the procedure of Rybinskaya *et al.*[5] {48% aq. HBF_4, $[Mn(CO)_4Cl]_2$, $(CF_3CO)_2O$, premixed at 0 °C then refluxed, 3 h; this reaction does not require exclusion of air}. Coupling of the sodium phenoxide from (**12**) with (**13**), in the presence of silver tetrafluoroborate¶ afforded complex (**14**) in 94% yield (Scheme 3). Demetallation of (**14**) (MeCN, room temp., overnight) gave (**15**) which was shown to be of 70% e.e. by n.m.r. Reaction of (**14**) with the Schöllkopf nucleophile (**2**) at −78 °C was again somewhat problematic [extensive demetallation of (**14**)], but gave satisfactory yields of the dienyl complex provided an excess of the nucleophile was used. Direct oxidation of the crude intermediate dienyl complex [*N*-bromosuccinimide, (NBS), Et_2O, room temp.] gave the diaryl ethers (**16**) and (**17**) as a separable 3:1 mixture in 50% overall yield, and hydrolysis of (**16**) afforded (**18**) in 95% yield. Similarly, (**17**) was converted to (**19**). N.m.r. studies on (**18**) and (**19**) indicated that no racemisation had occurred in the trisubstituted arylglycine side chain, and that the 3-aryloxyphenylglycine moiety was obtained in 50% enantiomeric excess, thereby indicating racemisation of this group to the extent of *ca.* 25—30% throughout the entire sequence. Comparison of (**18**) with ristomycinic acid (**20**) reveals that, with appropriate modification, this strategy is of potential value for constructing subunits of ristocetin A. It is noteworthy that racemisation is more pronounced using (**12**) than with the corresponding 4-hydroxyphenylglycine derivative.[1] Consequently, we anticipate that this would not be a problem in the construction of ristomycinic acid derivatives.

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3 See, for example: D. L. Boger, and D. Yohannes, *J. Org. Chem.*, 1988, **53**, 487; T. Teshima, M. Nishikawa, I. Kubota, T. Shiba, Y. Iwai, and S. Omura, *Tetrahedron Lett.*, 1988, **29**, 1963; S. Nishiyama, Y. Suzuki, and S. Yamamura, *ibid.*, 1988, **29**, 559.
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¶ No reaction occurs between (**13**) and the phenoxide from (**12**) in the absence of silver tetrafluoroborate, presumably due to the deactivating effect of the methoxy substituent.