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Catalytic asymmetric synthesis of ethyl (1*R*,2*S*)-dehydrocoronamate

Martin E. Fox,[a,*] Ian C. Lennon[a] and Vittorio Farina[b]

[a]*Dowpharma, Chirotech Technology Ltd, a subsidiary of The Dow Chemical Company, Unit 162 Cambridge Science Park, Milton Road, Cambridge CB4 0GH, UK*
[b]*Department of Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877-0368, USA*

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Abstract—A synthesis of (1*R*,2*S*)-dehydrocoronamic acid ethyl ester was developed employing a regio- and enantioselective palladium-catalysed nucleophilic ring-opening of 3,4-epoxy-1-butene with a glycine anion equivalent as the key enantiodifferentiating step. The desired selectivity was achieved using Trost's naphthyl ligand. The subsequent activation of the free hydroxyl group and ring-closure by intramolecular S_N2 reaction gave the desired amino acid ethyl ester.

The cyclopropyl amino acid (1*R*,2*S*)-dehydrocoronamic acid (1-amino-2-vinylcyclopropane-1-carboxylic acid, vinyl-ACCA) **1a** is a component of biologically active molecules of interest to the pharmaceutical industry, especially hepatitis C viral NS3 protease inhibitors such as BILN 2061 (ciluprevir) **2**[1–3] and other representative examples such as **3**[4] and **4**[4,5] (Fig. 1). Owing to the wide occurrence of **1** as a component of this class of compound, we were interested in developing an efficient, scaleable asymmetric synthesis of this compound. In addition, cyclopropyl amino acids[6] in general are compounds of industrial importance, so such a synthesis could have broader industrial applicability.

A high-yielding, large-scale synthesis of racemic **1** has been developed employing a diastereoselective S_N2-S_N2' dialkylation of glycine anion equivalents with 2-butene-1,4-dielectrophiles such as *trans*-1,4-dibromo-2-butene (Scheme 1).[2] The single enantiomer was obtained by resolution. In principle, a catalytic, asymmetric synthesis

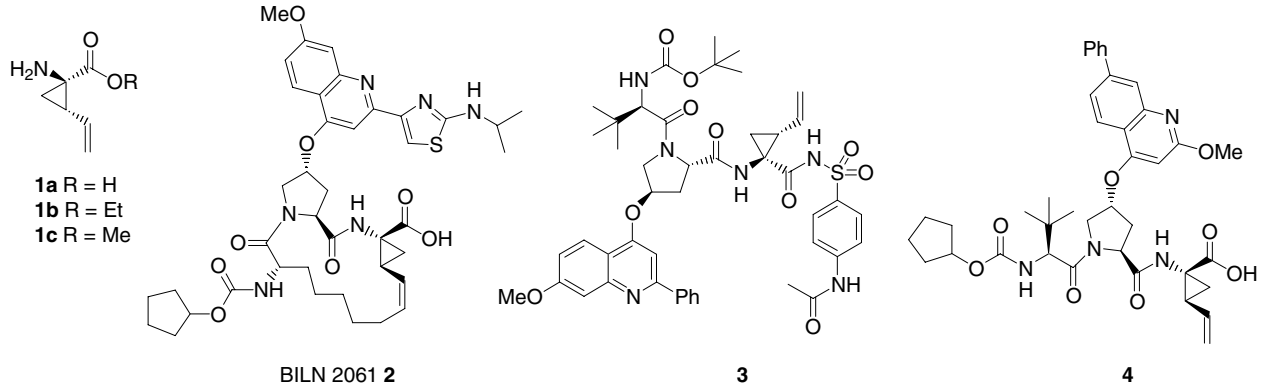

Figure 1. Hepatitis C protease inhibitors containing (1*R*,2*S*)-dehydrocoronamic acid.

Keywords: Palladium; Asymmetric catalysis; Allylic alkylation; 3,4-Epoxy-1-butene; Amino acids.
* Corresponding author. Tel.: +44 1223 728010; fax: +44 1223 506701; e-mail: mfox@dow.com

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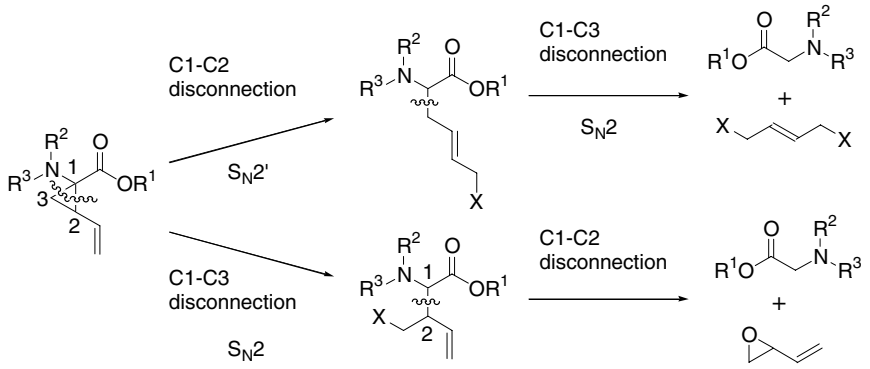
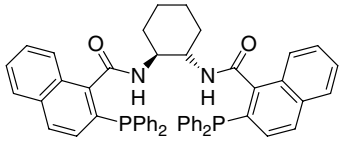


Scheme 1. Possible orders of C–C bond forming steps in cyclopropanation of a glycine anion equivalent.

has the potential to achieve a greater overall efficiency than a resolution-based synthesis. Therefore, we were attracted to this possibility. Asymmetric palladium-catalysed versions of the racemic synthesis described above have been reported.[7–9] However, these gave a low enantiomeric excess, and in some cases[7,8] also required the use of a chiral auxiliary. We considered an alternative strategy (Scheme 1) involving reversal of the order of C–C bond-forming steps in the overall cyclopropanation sequence such that instead of forming the C1–C3 bond followed by C1–C2, the C1–C2 bond is formed first, followed by C1–C3. In this analysis, the nucleophilic addition of a glycine anion equivalent to a (3-butene-1-ol)-2-yl electrophile is required in the first step.

We considered that this could be achieved by palladium-catalysed nucleophilic ring-opening of 3,4-epoxy-1-butene. In this asymmetric allylic alkylation reaction, Trost's naphthyl ligand **5** (Fig. 2) is uniquely capable,[10–12] giving exclusively the branched adduct in 80–90% enantiomeric excess with both oxygen and nitrogen-based nucleophiles. By analogy to the previously described examples, we expected to be able to achieve selectivity for the branched product in the addition of carbon nucleophiles, such as a glycine anion equivalent, as required for the synthesis of dehydrocoronamic acid **1**.

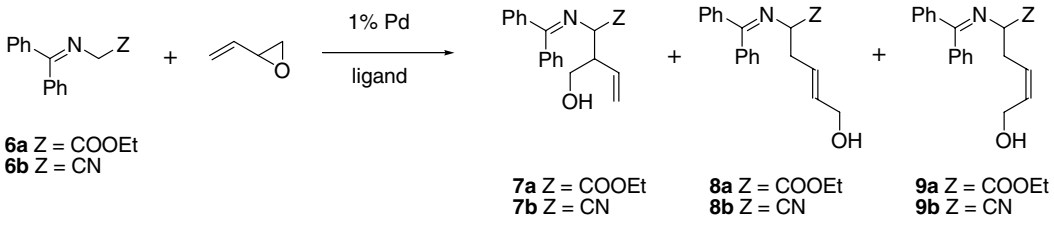


(*S*,*S*)-**5**

Figure 2. Trost's naphthyl ligand.

After this enantiodifferentiating step, closure of the 3-membered ring by intramolecular S$_N$2 reaction would give the desired cyclopropyl amino acid. In the intermolecular C–C bond forming step, two stereogenic centres are formed giving rise to two diastereoisomers. In the cyclisation step, C1 will be deprotonated to give a planar enolate intermediate, and this stereocentre will be reformed during the intermolecular alkylation. Thus, the stereochemistry obtained at this centre in the asymmetric allylic alkylation reaction is not critical. However, the C2 centre is unaffected in the cyclisation reaction and is carried through unchanged into the product. Control over the stereochemistry of the C2 centre results from the facial selectivity of bond-formation at C3 of the 3,4-epoxy-1-butene in the asymmetric allylic alkylation reaction. From the literature precedent with other nucleophiles, the (*S*,*S*)-enantiomer of ligand **5** was expected to provide the (*S*)-stereochemistry at this centre as required to give (1*R*,2*S*)-dehydrocoronamic acid.

We examined the reaction of two protected glycine equivalents; glycine ethyl ester benzophenone imine **6a** and 2-aminoacetonitrile benzophenone imine **6b** with 3,4-epoxy-1-butene using both chiral and achiral palladium catalysts. Three potential products are possible in this reaction, the desired branched product **7** and the trans- and cis-linear products **8** and **9**. The products obtained were strongly dependent on the ligands used (Scheme 2, Table 1). With simple achiral ligands, we obtained similar results to Mazón et al.,[13] with only linear products **8** and **9** being obtained. There was little or no selectivity for the double bond geometry. In contrast, Trost's naphthyl ligand gave entirely the branched



6a Z = COOEt
6b Z = CN

7a Z = COOEt
7b Z = CN

8a Z = COOEt
8b Z = CN

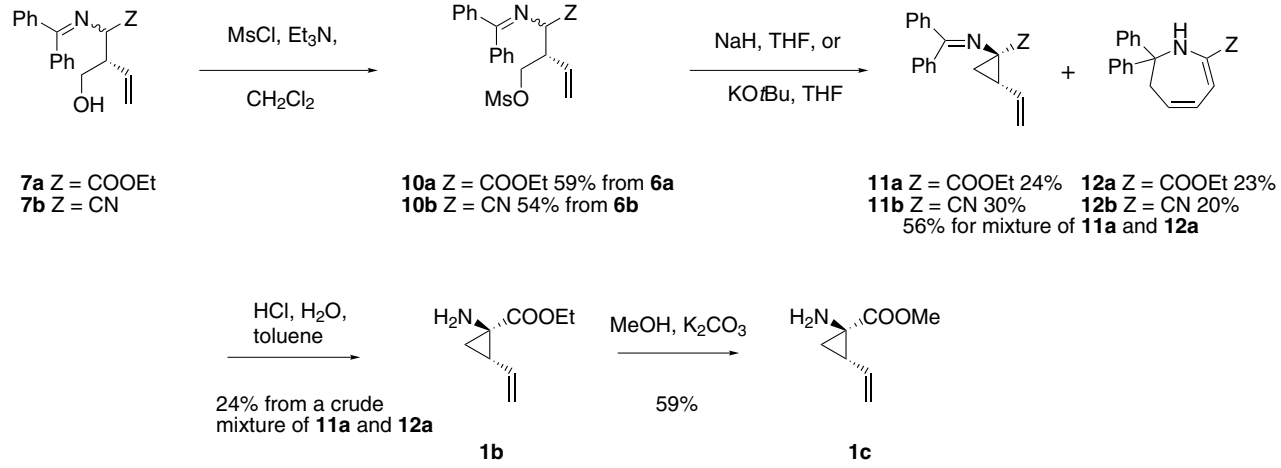
9a Z = COOEt
9b Z = CN

Scheme 2. Reaction of protected glycine equivalents with 3,4-epoxy-1-butene.

Table 1. Reaction of protected glycine equivalents with 3,4-epoxy-1-butene

Z	Pd source	Ligand	Solvent	Ligand/Pd molar ratio	Branched **7**%	*trans*-**8**%	*cis*-**9**%
COOEt	$Pd(OAc)_2$	PPh_3	THF	4	0	50	50
COOEt	$Pd(OAc)_2$	DPPE	THF	2	0	44	56
COOEt	$(allylPdCl)_2$	(*S*,*S*)-**5**	CH_2Cl_2	2.5	100	0	0
CN	$(allylPdCl)_2$	(*S*,*S*)-**5**	CH_2Cl_2	2.5	100	0	0

Product ratios were determined by ^1H NMR.



Scheme 3. Cyclisation of branched adducts to derivatives of (1*R*,2*S*)-dehydrocoronamic acid **1**.

product **7**. The ratio of diastereoisomers obtained was 3:2 for both nucleophiles. However, as discussed earlier, this ratio is not important in achieving a high enantiomeric excess in the synthesis of dehydrocoronamic acid by this route; it is the control over the C2 stereocentre which is of greater significance.

The branched adducts **7** were cyclised to derivatives of dehydrocoronamic acid by mesylation of the primary alcohol followed by treatment with sodium hydride or potassium *tert*-butoxide (Scheme 3). An approximately 1:1 mixture of the desired cyclopropane **11** and 2,3-dihydroazepine **12** resulting from facile aza-Cope rearrangement of the opposite diastereoisomer was obtained with both nitrile[7–9] and ester substrates. The mixture was readily separated by chromatography. The benzophenone imine protecting group of **11a** was cleaved by treatment with aqueous hydrochloric acid; conditions under which the 2,3-dihydroazepine was unaffected. Thus, by treatment of a toluene solution of the crude mixture of **11a** and **12a** with aqueous hydrochloric acid, the resulting cyclopropyl amino ester **1b** was extracted into the aqueous phase, leaving the unreacted dihydroazepine **12a** in the organic phase. Hence, it was possible to isolate amino ester **1b** from this mixture without recourse to chromatography. The more demanding nitrile to ester conversion required for **11b** was not attempted. In order to determine the enantiomeric excess, ethyl ester **1b** was converted to methyl ester **1c**, for which we were able to develop a chiral GC assay.[14] Thus, the absolute stereochemistry of the major enantiomer was shown to be (1*R*,2*S*)[15] and the enantiomeric excess to be 88%. The facial selectivity in the palladium-catalysed asymmetric allylic alkylation reaction is thus the same and the enantiomeric excess compares closely to the values obtained in other reactions of 3,4-epoxy-1-butene using ligand (*S*,*S*)-**5**.

Thus, we have demonstrated a concise catalytic asymmetric synthesis of dehydrocoronamic acid ethyl ester 1b using a novel strategy. We believe that with improvements to the selectivity in the cyclisation step and with an upgrade in enantiomeric excess, for example by crystallisation as a suitable salt, this route has the potential to provide an efficient synthesis of this important molecule.

Acknowledgement

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14. Sample: *N*-TFA derivative in ethyl acetate. Column: Chiraldex ATA 30 m × 0.25 mm. Carrier gas: Helium at 14 psi. Detection: FID at 200 °C. Injector temperature: 200 °C. Oven temperature: 60 °C for 5 min to 170 °C at 10 °C/min, hold for 5 min. Retention times: (1*R*,2*S*) 15.50 min; (1*S*,2*R*) 16.09 min.
15. By comparison with a sample made by methods described in Ref. 2.