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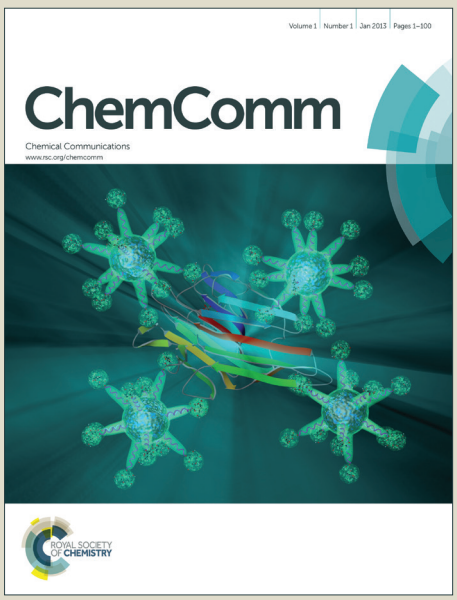

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ARTICLE TYPE

Dynamic Kinetic Resolution of Dehydrocoronamic Acid

David A. Chaplin,[a] Martin E. Fox*[a] and Sebastian H. B. Kroll[a]

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Dehydrocoronamic acid can be racemised by dehydration of an *N*-acyl derivative to an azlactone, which undergoes facile racemisation. For the *N*-trifluoroacetyl derivative, the racemisation process was combined with an enzymatic resolution, to achieve a dynamic kinetic resolution process by which the racemate can be converted to either enantiomer.

A family of Hepatitis C NS3 NS4A protease inhibitors which contain the common chiral motif (1*R*, 2*S*)-dehydrocoronamic acid **1** (Figure 1) comprises several antiviral drugs and developmental drug candidates (Figure 2).[1-9]

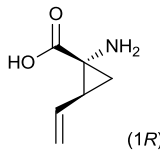


Figure 1 (1*R*, 2*S*)-Dehydrocoronamic acid.

Efficient synthesis of this densely functionalised quaternary amino-acid as a single enantiomer is challenging. However, a concise route to the racemate has been developed,[10,11] and routes to the single enantiomer based on resolution of both the racemate[10] and a malonate precursor[12] have been described. Synthesis from the chiral pool material butane-1,2,4-triol[13] and asymmetric routes employing asymmetric alkylation under chiral phase-transfer catalysis[11] and palladium-catalysed asymmetric allylic alkylation[14] have also been published. We reasoned that if a method for racemisation of the off-isomer could be found, this could be combined with the established racemic synthesis and a method of resolution to provide an overall high-yielding synthesis of this increasingly commercially important compound. On dehydration with DCC, as an entry to subsequent coupling reactions, amide derivatives of dehydrocoronamic acid **5** cleanly give azlactones **6** (Scheme 1). Subsequent methanolysis of **6** gives the corresponding methyl esters **7**. To our surprise, we discovered the enantiomeric excess of the product ester was lower than that of the starting acid.

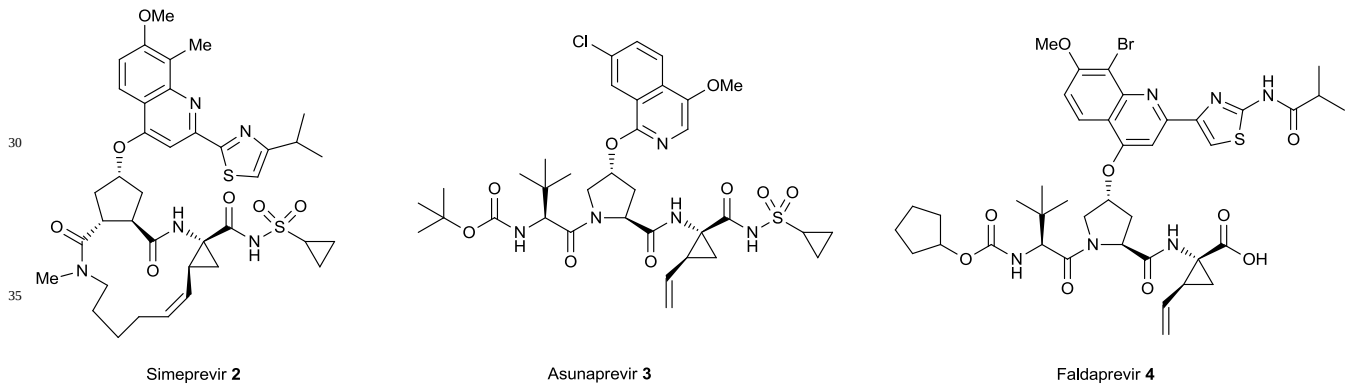
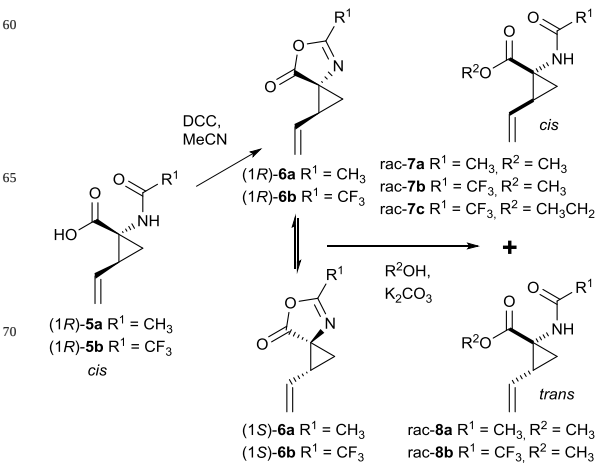
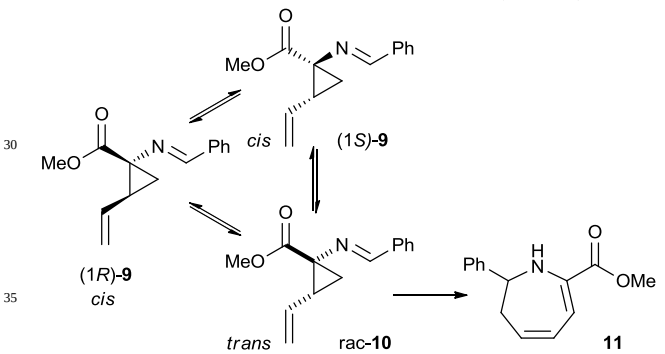


Figure 2. Examples of Hepatitis C NS3 NS4A protease inhibitors.



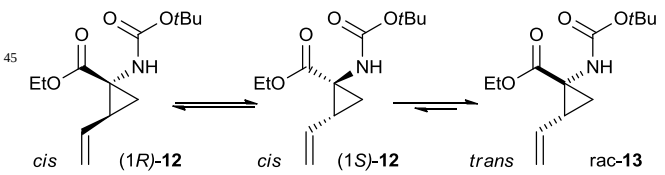
Scheme 1. Racemisation of dehydrocoronamic acid azlactones.

The rate of racemisation was strongly influenced by the nature of the amide group. Thus, the single enantiomer methyl azlactone **6a** racemised[‡] very slowly at room temperature in acetonitrile, and with $t_{1/2}$ of 60 minutes at 80 °C. Azlactone **6b** with an electron-withdrawing 3-trifluoromethyl substituent racemised more readily, with $t_{1/2}$ of 7.5 h at 15 °C in acetonitrile. In addition to racemisation, slower *cis*/*trans* isomerisation (Schemes 1 and 4) took place. This was detectable both by NMR and by chiral GC after methanolysis, which showed the *trans*-isomer **8** formed to be racemic. Rates of *cis*/*trans* isomerisation of **6a** and **6b** were almost identical at 80 °C in acetonitrile. Hence the relative rates of racemisation to *cis*/*trans* isomerisation were lower for **6a** (8.5:1 at 80 °C in acetonitrile) than **6b** (165:1 at 15 °C). After *in-situ* formation of **6a** from (1*R*)-**5a**, heating for 4 h at 80 °C, then methanolysis at ambient temperature, racemic **7a**+**8a** (6:1) was isolated in quantitative yield. For (*1R*)-**6b**, after 1 day at 15 °C, near-racemic (12% ee) **7b** + **8b** (189:1) was isolated in 70% yield. This behaviour was in marked contrast to the thermal isomerisation of other dehydrocoronamic acid derivatives, for example, the benzaldehyde imine **9**,[9,10] where racemisation was much slower than *cis*/*trans* isomerisation (Scheme 2). For this compound, after 120 minutes at 80 °C in toluene, the enantiomeric excess was 98.1%, but the ratio of imine **9** to dihydroazepine **11**, formed by [3,3]-sigmatropic isomerisation of the *trans*-isomer **10**[10,11] was 5:1 (66% de).



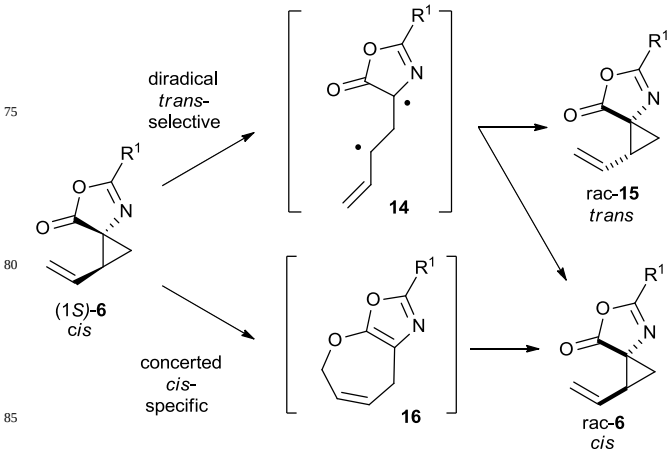
Scheme 2. Isomerisation of dehydrocoronamic ester imine.

Likewise, the *N*-BOC, *cis*-ethyl ester **12** underwent more rapid *cis*/*trans* isomerisation than racemisation, reaching 90% ee and 38:62 *cis*/*trans* after 16 h in *o*-dichlorobenzene at 150 °C.



Scheme 3. Isomerisation of *cis*-*N*-BOC dehydrocoronamic acid ethyl ester.

These observations can be rationalised if a *trans*-selective thermal isomerisation mechanism is possible for all dehydrocoronamic acid derivatives, but a different and *cis*-stereospecific isomerisation is possible for azlactones **6** (Scheme 4). A diradical mechanism[15-17] is widely accepted for cyclopropane thermal isomerisation. For the intermediate **14**, C-C bond rotation is possible, hence this pathway would give the thermodynamically more stable *trans* isomer **15** as the main product. For the *cis*-stereospecific rearrangement, we propose a mechanism which proceeds by concerted [3,3]-sigmatropic oxadivinylcyclopropane rearrangement to an achiral dihydrooxepine intermediate **16**, for which C-C bond rotation is not possible. This mechanism should be energetically more favoured for azlactone **6** compared to other dehydrocoronamic acid derivatives owing to the stabilisation provided by the simultaneous formation of an aromatic oxazole heterocycle. Increasing the electron-withdrawing power of the azlactone substituent R^1 withdraws electron density from the C=O bond and destabilises the azlactone relative to the oxazole.



Scheme 4. Proposed mechanisms of azlactone isomerisation.

Evidence for this mechanism is provided by the ^{1}H NMR spectrum of **6b** (Figure 3), where in addition to the major signals which can be assigned to the cyclopropane structure, a minor set of four signals [δ_H (400 MHz, $CDCl_3$; Me_4Si) 6.18, (1 H, dt, J = 11.2, 5.2 Hz, OCH_2CH), 5.97 (1 H, dtt. J = 11.2, 5.9, 2.2 Hz, OCH_2CHCH), 4.72 (2H, d, J = 5.9 Hz, OCH_2) and 3.47(2 H, dd, J = 5.2, 2.2 Hz, $OCH_2CHCHCH_2$)] is observed in a 30:1 ratio which can be assigned to dihydrooxepine **16**, present as an equilibrium component.

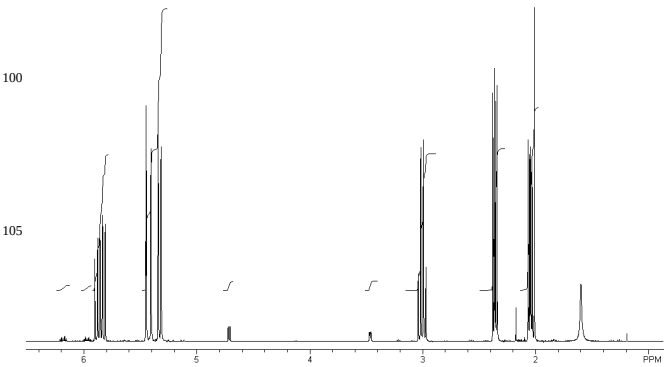
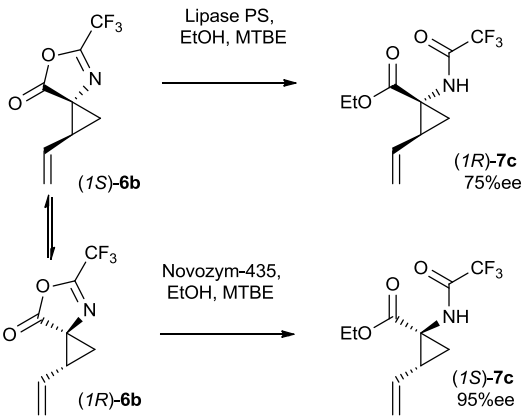


Figure 3. ^{1}H NMR spectrum of CF_3-azlactone **6b**.

Given the ready racemisation of trifluoromethyl azlactone **6b** at ambient temperature and the utility of trifluoroacetyl as a removable nitrogen protecting group,[18-21] we were able to apply this discovery to our objective of an asymmetric synthesis of dehydrocoronamic acid. The racemisation could be applied in a

resolution-based approach by recycle of the off-isomer of acid **5** to racemic ester **7** or acid **5**. The desired (1*R*)-ester was obtained by resolution of **7b** by enantioselective hydrolysis of the ester group of the (1*S*)-enantiomer with Subtilisin A, with an E value of around 100, sufficiently high for an efficient resolution. However, this enzyme also cleaved the trifluoroacetyl group to a significant extent, reducing the possible efficiency of the recycle of (1*S*)-**5b**. Dynamic kinetic resolution of azlactone **6** provides a more direct and attractive approach than resolution/recycle of ester **7**. Dynamic kinetic resolution of azlactones bearing a single 5-substituent, which can tautomerise to an enol form, by ring-opening with nucleophiles in the presence of a chiral catalyst is well-established.[22-26] Application of this concept to reaction of the 5,5-disubstituted azlactone **6b** with alcohols mediated by enzymes proved feasible (Scheme 5). On a 7.5 g scale, the isolated yield of rac-**6b** from rac-**5b** was 89%. In the dynamic kinetic resolution, ethanol gave the best combination of reactivity and selectivity. With Novozym-435 (immobilised *Candida antarctica* Lipase B) under optimised conditions, (100:1 *w*/*w* MTBE-ethanol at 25 °C) on a 1 g scale, (1*S*)-**7c** was obtained in 95% ee and 97% isolated yield after 11 days (E~40). For (1*R*)-**7c**, the isomer required for the antiviral compounds, the highest enantioselectivity was achieved with immobilised Lipase PS. On a 1 g scale, under the same conditions, 75% ee and 96% isolated yield was obtained after 18 days (E~7).



Scheme 5. Dynamic kinetic resolution of azlactone **6b**.

Conclusions

We have discovered a method for racemisation of dehydrocoronamic acid and applied this to the asymmetric synthesis of either enantiomer of this commercially significant molecule by enzyme mediated dynamic asymmetric kinetic resolution. A concerted [3,3]-sigmatropic mechanism is proposed for this isomerisation.

Notes and references

[a] *Chirotech Technology Centre, Dr Reddy's Laboratories EU Ltd., Unit 410 Cambridge Science Park, Milton Road, Cambridge, CB4 0PE, UK. Fax: 44(0)1223 506710; Tel: 44(0)1223 728010; E-mail: mfox@drreddys.com*

† Electronic Supplementary Information (ESI) available: Experimental procedures for preparation and isomerisation of **6a**, **6b** and **10**, isomerisation of **12**, resolution of **7b** and dynamic kinetic resolution of **6b**. GC analytical methods and chromatograms for **7a-c**, **12** and **13**. ^{1}H NMR spectra of **1**, **5a**, **5b**, **6a**, **6b**, **7a**, **7b**, **7c**, **9**, **11**, **12**, **13**, **15a**, **15b**. See DOI: 10.1039/b000000x/

‡ Enantiomeric excesses of **6** determined by methanolysis to ester **7** then chiral GC.

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