A Chiral Base Desymmetrisation–Ring-Closing Metathesis Route to Chiral Azaspirocycles: Synthesis of Core Structures Related to Pinnaic Acid and Halichlorine

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Received 18 July 2004

Abstract: A range of highly functionalised chiral azaspirocycles was synthesised, starting from a piperidine diester that is available in 90% ee from a chiral base desymmetrisation. The approach depends upon the use of Grignard addition reactions or a Claisen rearrangement to provide intermediates capable of undergoing ring-closing metathesis. A number of intermediates related to the core structure of pinnaic acid were synthesised by concise routes using the approach.

Key words: azaspirocycle, pinnaic acid, ring-closing metathesis

Natural products incorporating azaspirocyclic structures, such as the well known histrionicotoxin family [e. g. histrionicotoxin (**1**)], have long attracted the interest of synthetic chemists.[1] A more recently disclosed structure is pinnaic acid (**2**), which has stimulated substantial activity due to its potency as an inhibitor of cPLA$_2$ (phospholipase A$_2$).[2] The closely related alkaloid, halichlorine (**3**), found to inhibit VCAM-1 (vascular cell adhesion molecule-1), was isolated around the same time and has also sparked a great deal of interest (Figure 1).[3]

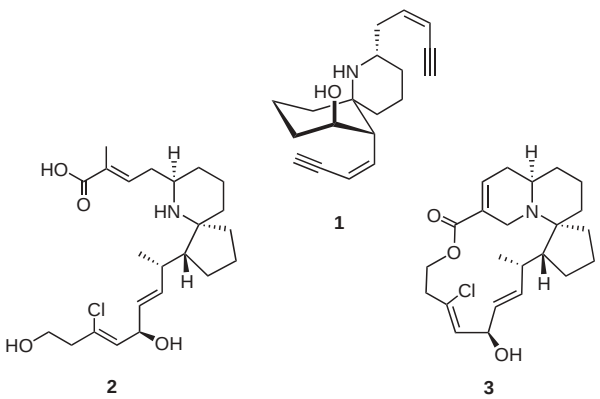


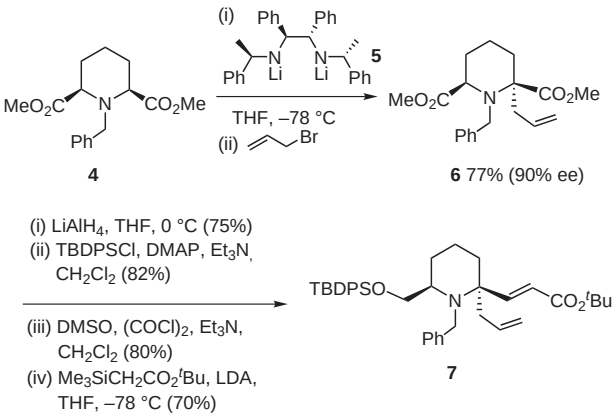
Figure 1

Since these compounds exhibit potentially useful biological activity, synthetic approaches, which deliver highly functionalised azaspirocycles, of various ring size combinations, in a stereocontrolled fashion are of intense current interest.[4–6]

SYNLETT 2004, No. 13, pp 2295–2298
Advanced online publication: 08.09.2004
DOI: 10.1055/s-2004-831335; Art ID: D19704ST

Some time ago we described a new type of chiral lithium amide base reaction, which provided chiral polyfunctional piperidines with high levels of stereocontrol.[7] In the present paper we describe how one such piperidine can be usefully transformed into a range of azaspirocyclic systems, with a focus on compounds closely related to the pinnaic acid core structure.[8]

The previously described desymmetrisation reaction involves enolisation of the readily available piperidine diester **4** with chiral base **5**, and subsequent alkylation to give products such as the allyl derivative **6**, Scheme 1.[9]



Scheme 1

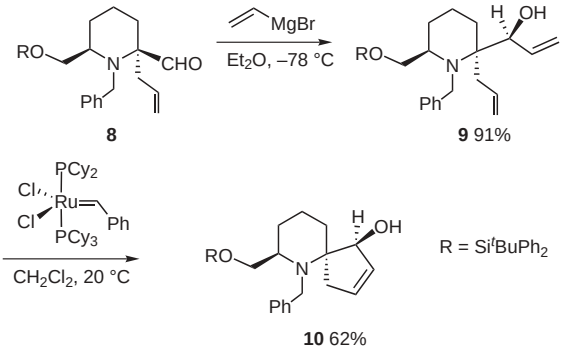
Subsequent differentiation of the ester functions was then carried out by reduction of **6** to the corresponding diol, selective protection of the less hindered primary alcohol, oxidation and Peterson olefination. This sequence provided quantities of α,β-unsaturated ester **7**, and we initially hoped to develop this compound to a spirocyclic system by establishing a novel cyclisation protocol for linking the terminus of the allyl group to the β-position of the enoate.

The first plan was to effect regioselective hydrometallation of the allylic appendage to give a terminal organometallic, which, on activation by transmetallation, would then undergo intramolecular Michael addition. In the event, a series of studies, focussed on the combination of initial hydroboration or hydrozirconation, followed by transmetallation chemistry using zinc or copper, failed to provide an effective means of ring-closure.[10,11]

As a back-up tactic we expected that conversion of the allyl group into a terminal halide, or similar, would allow

conventional 5-*exo*-*trig* radical mediated ring-closure, or perhaps a metal–halogen exchange with concomitant Michael addition. Again, we were unable to bring these ideas to fruition,[12] and were prompted to explore an alternative approach, which employs a key ring-closing metathesis step.

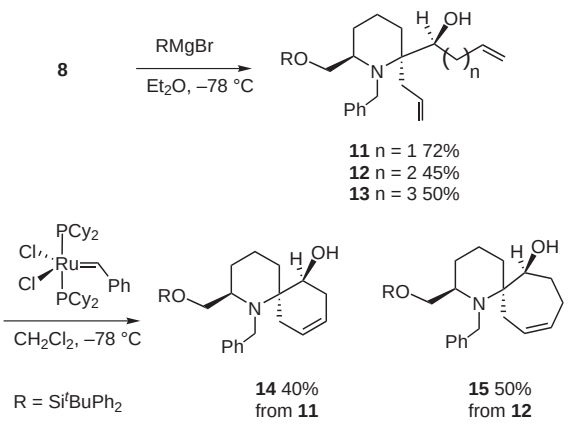
Aldehyde **8** (the product of Swern oxidation in Scheme 2) was found to undergo smooth addition reactions with vinyl magnesium bromide, providing access to secondary alcohol product **9** as single diastereoisomer, Scheme 2.



Scheme 2

The sense of induction at the new stereogenic centre in **9** was predicted from examination of molecular models, by assuming a least hindered approach on aldehyde **8** (see later), and was subsequently proved by X-ray analysis.[13]

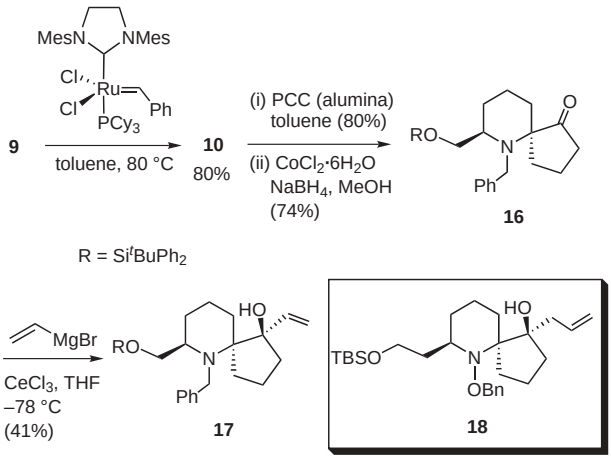
Diene **9**, on treatment with the first generation Grubbs catalyst underwent the desired ring-closure process to give allylic alcohol **10** in good yield. As shown in Scheme 3, we were also able to access the corresponding products **14** and **15** with the azaspiro[5,5]undecane and azaspiro[5,6]dodecane structures, respectively.



Scheme 3

These sequences are unoptimised, and we observed some competing aldehyde reduction in the Grignard addition step. Also, exposure of the extended diene **13** to the metathesis conditions did not result in formation of the desired 8-membered ring product.

The success of the diene metathesis route opens up a number of opportunities for progress towards natural products, including pinnaic acid. Firstly, we were able to carry out a range of further transformations of spirocyclic allylic alcohol **10**, as shown in Scheme 4.



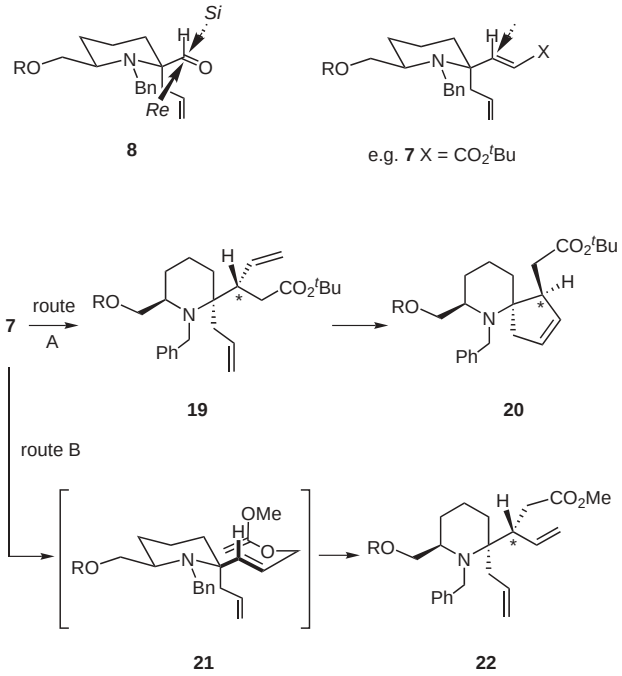
Scheme 4

We first established that the efficiency of ring-closing metathesis of **9** to give cyclopentene **10** was improved on changing to the 'second generation' Grubbs catalyst (similarly, the use of this catalyst gave **15** in a substantially improved yield of 85%). Applying a straightforward oxidation–conjugate-reduction sequence to allylic alcohol **10** then provided ketone **16**.[14] This ketone bears a striking resemblance to a racemic intermediate employed by Kibayashi in their recently disclosed synthesis of pinnaic acid.[4] In this synthesis Grignard addition reactions led to intermediate **18**. Our ketone underwent similar stereoselective additions, for example to provide allylic alcohol **17**, which may well be capable of being further transformed towards pinnaic acid via the Kibayashi approach.

Bearing in mind the apparent utility of the RCM process for spiro-annulation, we sought to devise flexible entries to appropriate dienes that would all enable access to more advanced intermediates towards pinnaic acid and halichlorine. Two such synthetic sequences, which pay special attention to addressing stereocontrol issues, are illustrated in Scheme 5.

Addition of Grignard reagents to aldehyde **8** had been shown to occur with high selectivity from the rear (*Si*) face as shown, the front face presumably being blocked by the *N*-benzyl substituent. It seemed possible that analogous selectivity might also be observed in addition to homologated systems, exemplified by unsaturated ester **7**. However, in the hope of anticipating either stereochemical outcome, we planned two stereocomplementary sequences designed to provide either epimer of the RCM precursor diene.

In the first sequence (route A) Michael addition of a vinylic unit to α,β-unsaturated ester **7** might provide **19**, which would undergo RCM to give the spirocyclic product **20**

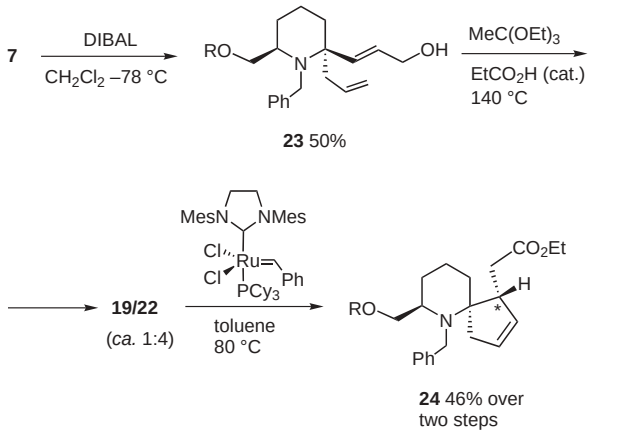


Scheme 5

with the desired stereochemistry for pinnaic acid and halichlorine.

Alternatively, we could reduce **7** to the corresponding allylic alcohol and then perform a Claisen rearrangement (route B) to give **22**, which should give complementary stereochemistry at the crucial new stereocentre (C*) compared to route A, provided that reaction followed the pattern identified for **8**.

In the event we explored route B first, since preliminary attempts to apply cuprate chemistry to enoate **7** were not fruitful. Thus, reduction of ester **7** with DIBAL gave allylic alcohol **23**, which was subsequently transformed into product **24**,[15] having the azaspiro core with the desired carboxymethyl side chain, by the Johnson ortho-ester Claisen rearrangement,[16] followed by ring closing metathesis, Scheme 6.



Scheme 6

The process provides the final spirocycle **24**, which was assigned as the undesired epimer for pinnaic acid synthesis,[17] as predicted by our simple model.

This route to substituted azaspirocycle **24** requires only seven steps from the initial chiral base product **6**, and opens up several potential avenues to the natural systems, based on the stereochemical model that we have established. Firstly, we expect that the cuprate addition process (**7** to **19**) will provide the required RCM precursor, and we intend preparing less hindered acceptors, and employing cuprate reagents known to be effective with hindered systems. Secondly, effective inversion of the undesired stereochemistry in **24** can be envisaged by a dehydrogenation (or C=C migration)–hydrogenation sequence, provided the stereochemical model holds.

In conclusion, the present results show that a range of functionalised and substituted azaspirocycles can be generated, starting from the non-racemic piperidine **6**. Further developments of the strategy are expected to provide concise and versatile syntheses of pinnaic acid and close analogues.

Acknowledgment

We thank The Engineering and Physical Sciences Research Council (EPSRC) and the University of Nottingham for support of TH. We thank Nick Goldspink for preliminary work.

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(9) In ref.[8], Clive reports only a 69% ee was possible in the preparation of **7**, whereas we have observed 90–95% ee in several runs. We are presently in communication with Professor Clive in order to resolve this disparity.
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(12) It appears that the basic tertiary amine interferes with the organometallic chemistry; and in the radical reactions we suspected 1,6-hydrogen atom abstraction from the N-CH_2Ph group.
(13) Analysis of allylic alcohol **10**, in the form of its 4-nitrobenzoate ester revealed the stereochemistry shown. We thank Dr A. J. Blake of this school for this result, full details of which will be published later.
(14) Data for ketone **16**: $[\alpha]_D^{28}$ –6.2 (*c* 1.0 in $CHCl_3$). IR ($CDCl_3$): ν_{max} = 2930 (s), 2858 (s), 1737 (s), 1588 (m), 1453 (m), 1362 (m), 1089 (s) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.96 (9 H, s, *t*-Bu), 1.26–1.30 (1 H, m), 1.50–1.54 (3 H, m), 1.67–1.78 (2 H, m), 1.97–2.06 (4 H, m), 2.14 (1 H, m, 2-H), 2.31 (1 H, m, 2-H), 2.61 (1 H, m, 7-H), 2.89 (1 H, dd, *J* = 9.9, 8.4 Hz, CH_2OSi), 3.21 (1 H, d, *J* = 15.9 Hz, NCH_2Ph), 3.33 (1 H, d, *J* = 15.9 Hz, NCH_2Ph), 3.56 (1 H, dd, *J* = 9.9, 3.8 Hz, CH_2OSi), 7.07–7.14 (3 H, m, Ar), 7.23–7.27 (2 H, m, Ar), 7.27–7.35 (4 H, m, Ar), 7.36–7.45 (6 H, m, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.7 (CH_2), 19.2 (C), 19.8 (CH_2), 25.9 (CH_2), 26.9 (CH_3), 29.3 (CH_2), 31.3 (CH_2), 37.2 (CH_2), 56.9 (CH_2), 62.3 (CH), 67.6 (CH_2), 71.6 (C), 126.3 (CH), 127.2 (CH), 127.5 (CH), 127.8 (CH), 129.5 (CH), 129.5 (CH), 133.7 (C), 133.9 (C), 135.5 (CH), 135.6 (CH), 142.0 (C), 220.0 (C=O). HRMS (APCI): *m/z* calcd for $C_{33}H_{42}NO_2Si$ [M + H]: 512.2985; found: 512.2999.
(15) The Claisen rearrangement gave a mixture of intermediates, assigned as **19**/**22** in a ca. 1:4 ratio. So far we have been able to isolate only the metathesis product derived from the major component. Data for ester **24**: $[\alpha]_D^{27}$ –4.2 (*c* 1.0 in $CHCl_3$). IR ($CDCl_3$): ν_{max} = 2957 (s), 2930 (s), 2858 (s), 1726 (s), 1588 (w), 1427 (m) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.96 (9 H, s, *t*-BuSi), 1.17 (3 H, t, *J* = 7.3 Hz, Me), 1.45–1.69 (5 H, m), 1.97 (1 H, br d, *J* = 13.0 Hz), 2.13 (1 H, dd, *J* = 14.9, 10.7 Hz, CH_2CO_2), 2.25 (1 H, dd, *J* = 17.2, 2.3 Hz, 4-H), 2.54 (1 H, d, *J* = 17.2 Hz, 4-H), 2.58–2.63 (2 H, m, 7-H and CH_2CO_2), 3.05 (1 H, m, 1-H), 3.07 (1 H, dd, *J* = 9.9, 7.6 Hz, CH_2OSi), 3.30 (1 H, d, *J* = 17.4 Hz, NCH_2Ph), 3.55 (1 H, dd, *J* = 9.9, 3.8 Hz, CH_2OSi), 3.85 (1 H, d, *J* = 17.4 Hz, NCH_2Ph), 4.05 (2 H, m, OCH_2Me), 5.56 (1 H, br dd, *J* = 6.1, 1.9 Hz, 2-H), 5.71 (1 H, br dd, *J* = 6.1, 2.3 Hz, 3-H), 7.10 (1 H, m, Ar), 7.14–7.19 (4 H, m, Ar), 7.28–7.31 (4 H, m, Ar), 7.36–7.40 (2 H, m, Ar), 7.42–7.45 (4 H, m, Ar). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2 (CH_3), 19.2 (C), 20.2 (CH_2), 27.0 (CH_3), 29.9 (CH_2), 33.1 (CH_2), 35.7 (CH_2), 37.6 (CH_2), 49.8 (CH), 53.9 (CH_2), 60.3 (CH_2), 63.6 (CH), 68.1 (CH_2), 68.7 (C), 125.9 (CH), 126.8 (CH), 127.6 (CH), 127.9 (CH), 129.5 (CH), 132.8 (CH), 133.8 (C), 133.9 (C), 135.5 (CH), 135.6 (CH), 143.2 (C), 173.4 (C=O). HRMS (APCI): *m/z* calcd for $C_{37}H_{48}NO_3Si$ [M + H]: 582.3403; found: 582.3398.
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(17) This assignment is based on gradient NOE enhancements seen between the methine at C-1 of the cyclopentene (C*) and the methylene of the N-Bn group. By contrast no such enhancement to the methylene of the CH_2CO_2Et substituent was seen.