

## Synthetic Approaches to the Alkaloids of the Ancistrocladaceae: Control of the Diastereoisomer Excess in the Synthesis of Axially Chiral Biaryls: a Synthesis of (–)-Ancistrocladinine

Mark A. Rizzacasa and Melvyn V. Sargent\*

Department of Organic Chemistry, The University of Western Australia, Nedlands, Western Australia, 6009

An attempt is made to delineate the factors which control the diastereoisomeric excess in the reactions of 2,6-disubstituted phenyl Grignard reagents with the naphthyloxazoline **2**; advantage is taken of the results in a synthesis of the *Ancistrocladus* alkaloid (–)-ancistrocladinine **19**.

The synthesis of axially chiral biaryls is an area of intense activity and efforts have been directed towards both the synthesis of these molecules for use in asymmetric synthesis,<sup>1</sup> and naturally occurring examples.<sup>2</sup>

We have used the reaction of an aryl Grignard reagent with a chiral *o*-methoxyaryloxazoline to generate chiral aryl naphthalenes for use in the total synthesis of the *Ancistrocladus* alkaloids.<sup>3</sup> The factors which govern the diastereoisomeric ratios in such reactions are poorly understood. For example, in the reaction of the naphthyloxazoline **1** with 1-naphthylmagnesium bromide and with 2-methyl-1-naphthylmagnesium bromide the predominant product is the atropisomer of the same chirality, whereas with 2-methoxy-1-naphthylmagnesium bromide the atropisomer of the opposite chirality predominates.<sup>4</sup> In the first instance steric effects appear to control the stereochemical outcome whereas in the other instance it is thought that chelation of the methoxy

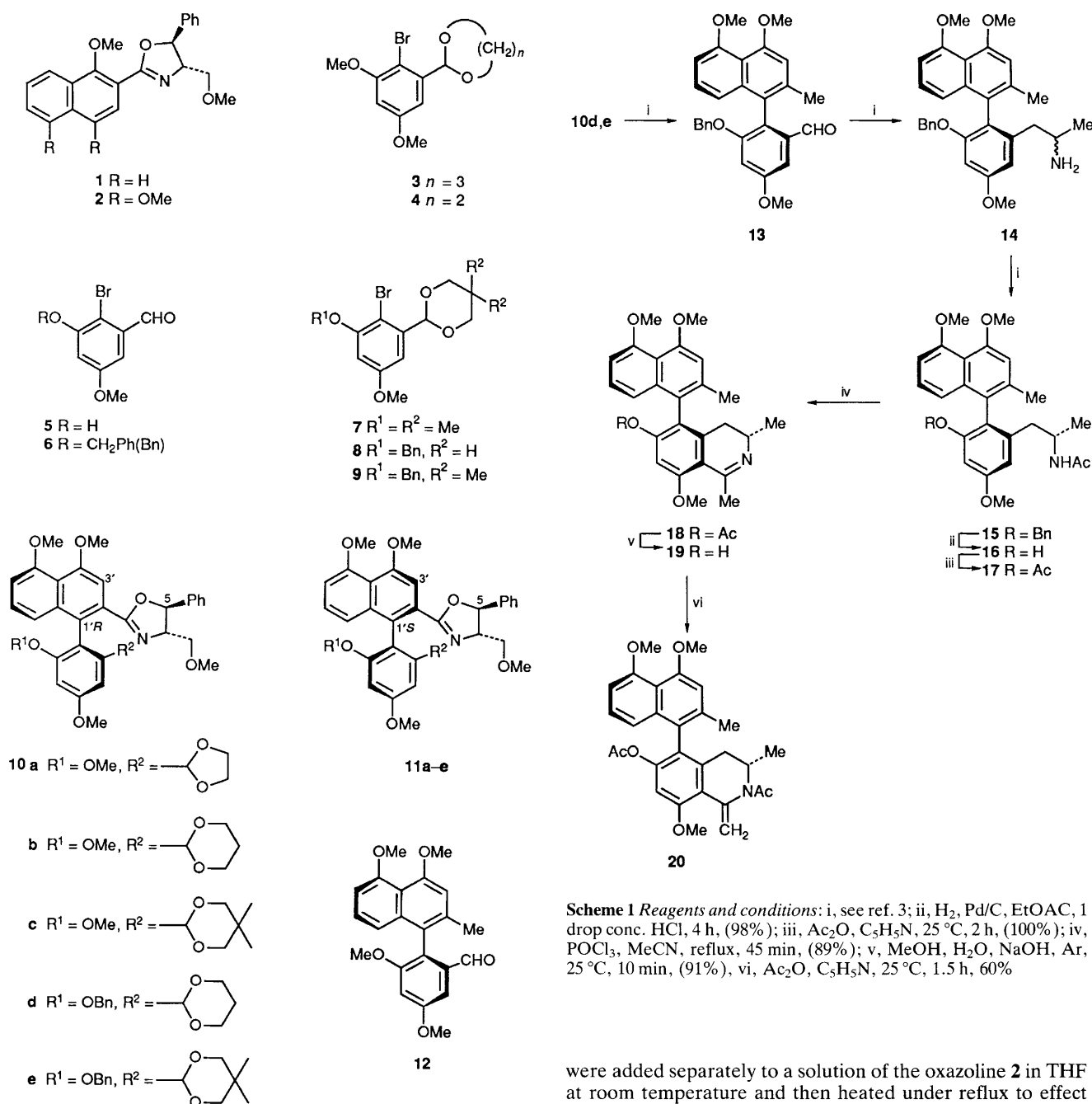
group of the Grignard reagent to the magnesium in the transition state is the dominant factor.<sup>4</sup> The results of attempts to apply this method to the synthesis of 2,2',6,6'-tetrasubstituted biphenyls have been poor. The yields were low because of steric crowding and the low diastereoselectivity was attributed to the small size difference between the substituents in the 2,6-disubstituted phenyl Grignard reagents.<sup>5</sup>

Because of our interest in the synthesis of the *Ancistrocladus* alkaloids we have studied the reaction of the chiral oxazoline **2**<sup>3</sup> with a variety of 2,6-disubstituted phenyl Grignard reagents. The bromide **3** was available from our previous work and the homologues **4** and **7**<sup>†</sup> were prepared in

<sup>†</sup> New compounds gave satisfactory elemental analyses or high resolution mass spectral molecular ions and spectra in accord with the assigned structures.

**Table 1** Reaction of the oxazoline **2** with Grignard reagents

Compound <b>10, 11</b>	Yield (%)	Chemical shifts <b>10</b>		Ratio		D.e. <sup>a</sup> (%)	Chemical shifts <b>11</b>	
		$\delta$ -H-5	$\delta$ -H-3'	<b>10</b>	<b>11</b>		$\delta$ -H-5	$\delta$ -H-3'
<b>a</b>	77	5.13	7.50	42	58	16	5.22	7.35
<b>b</b>	65	5.05	7.52	69	31	38	5.17	7.35
<b>c</b>	72	5.06	7.49	70	30	40	5.16	7.36
<b>d</b>	64	5.05	7.52	77	23	54	5.16	7.38
<b>e</b>	69	5.05	7.49	88	12	76	5.16	7.40

<sup>a</sup> D.e. = diastereoisomeric excess.

**Scheme 1** Reagents and conditions: i, see ref. 3; ii, H<sub>2</sub>, Pd/C, EtOAc, 1 drop conc. HCl, 4 h, (98%); iii, Ac<sub>2</sub>O, C<sub>5</sub>H<sub>5</sub>N, 25 °C, 2 h, (100%); iv, POCl<sub>3</sub>, MeCN, reflux, 45 min, (89%); v, MeOH, H<sub>2</sub>O, NaOH, Ar, 25 °C, 10 min, (91%); vi, Ac<sub>2</sub>O, C<sub>5</sub>H<sub>5</sub>N, 25 °C, 1.5 h, 60%

a similar fashion.<sup>3</sup> The known aldehyde **5**<sup>6</sup> was benzylated and the product **6** was converted into the cyclic acetals **8** and **9**.<sup>†</sup> A solution of each bromide in tetrahydrofuran (THF) was converted into its Grignard reagent (2 mol equiv.) and these

were added separately to a solution of the oxazoline **2** in THF at room temperature and then heated under reflux to effect reaction. The products (see Table 1) were separated by flash chromatography.

Diastereoisomer **10b**<sup>†</sup> has previously been degraded to the aldehyde **12**; diastereoisomer **11a** was degraded by the same methodology to the atropisomer<sup>†</sup> of **12**, m.p. 155–157 °C, [ $\alpha$ ]<sub>D</sub><sup>19</sup> –7.1° (THF, *c* 2.97). These atropisomers are of known

absolute stereochemistry since they have been converted into (–)-*O*-methylancistrocladine and (+)-*O*-methylhamatine, respectively.<sup>3</sup> The diastereoisomers **10d** and **10e**<sup>†</sup> (see Scheme 1) were both converted into the aldehyde **13**,<sup>†</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> +23.2° (CHCl<sub>3</sub>, *c* 2.57) which was converted into (–)-ancistrocladinine **19**, a minor alkaloid of *Ancistrocladus heyneanus* Wall.<sup>7</sup> It is pertinent to note the difference in the chemical shifts of the 3'- and 5-protons in the <sup>1</sup>H NMR spectra of the compounds belonging to each atropisomeric series. These differences were used to assign the absolute configurations of compounds **10c** and **11c**.<sup>†</sup>

In the case of the five-membered acetal **4** the 1'-(*S*) atropisomer predominates but for all the six-membered acetals the 1'-(*R*) atropisomer predominates. Increasing the bulk of both the 2- and 6-substituents in the Grignard reagent enhances the diastereoisomeric excess. Since both the 2- and 6-substituents contain oxygen atoms which could chelate with the magnesium in the transition state<sup>4</sup> it appears that the steric bulk of the substituents is more important. It was observed that the reactions involving the Grignard reagents with benzyloxy substituents were slower (18 h) than those involving methoxy substituents (5 h). Reaction rate, controlled by the bulk of the 2- and 6-substituents therefore appears to influence the diastereoisomeric excess.

The aldehyde **13** (see Scheme 1) was converted by the same methodology as that used previously<sup>3</sup> into the amine **14**. Resolution and acetylation, as before,<sup>3</sup> gave the amide **15**,<sup>†</sup> [ $\alpha$ ]<sub>D</sub><sup>20</sup> –27.9° (THF, *c* 0.97). This compound was deprotected and the resulting phenol **16**,<sup>†</sup> m.p. 105–108 °C, [ $\alpha$ ]<sub>D</sub><sup>19</sup> –52.7° (THF, *c* 0.42), was acetylated. The crude *N,O*-acetyl compound **17** on Bischler–Napieralski cyclization afforded the *O*-acetyl compound **18** which on hydrolysis afforded

(–)-ancistrocladinine **19**, m.p. 255–258 °C decomp. (lit.,<sup>7</sup> 235–238 °C decomp.) which was characterized as its diacetate **20**,<sup>†</sup> m.p. 198–200 °C, [ $\alpha$ ]<sub>D</sub><sup>18</sup> +72.0° (CHCl<sub>3</sub>, *c* 0.88) {lit.,<sup>7</sup> 204–206 °C, [ $\alpha$ ]<sub>D</sub> +88.62° (CHCl<sub>3</sub>, *c* 3.23)}.

Since naturally occurring (–)-ancistrocladinine **19** has been converted into (–)-ancistrocladine<sup>8</sup> this synthesis also constitutes a formal total synthesis of this alkaloid. The aldehyde **13** is therefore a pivotal intermediate in the synthesis of chiral 5-1'-linked *Ancistrocladus* alkaloids.

Received, 6th September 1990; Com. 0/04061D

## References

- 1 H. Hotta, T. Suzuki and S. Miyano, *Chem. Lett.*, 1990, 143, and references therein.
- 2 A. I. Meyers, J. R. Flisak and R. A. Aitken, *J. Am. Chem. Soc.*, 1987, **109**, 5446; G. Bringmann, J. R. Jansen, H. Reuscher, M. Rübenacker, K. Peters and H. G. von Schnering, *Tetrahedron Lett.*, 1990, 643, and references therein.
- 3 M. A. Rizzacasa and M. V. Sargent *J. Chem. Soc., Chem. Commun.*, 1990, 894.
- 4 A. I. Meyers and K. A. Lutomski, *J. Am. Chem. Soc.*, 1982, **104**, 879.
- 5 A. I. Meyers and R. J. Himmelsbach, *J. Am. Chem. Soc.*, 1985, **107**, 682.
- 6 K. Wähälä, I. Ojanperä, L. Häyri and T. A. Hase, *Synth. Commun.*, 1987, **17**, 137.
- 7 T. R. Govindachari, P. C. Parthasarathy and H. K. Desai, *Indian J. Chem.*, 1971, **9**, 1421.
- 8 T. R. Govindachari, K. Nagarajan, P. C. Parthasarathy, T. G. Rajagopalan, H. K. Desai, G. Kartha, S. L. Chen and K. Nakanishi, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1413.