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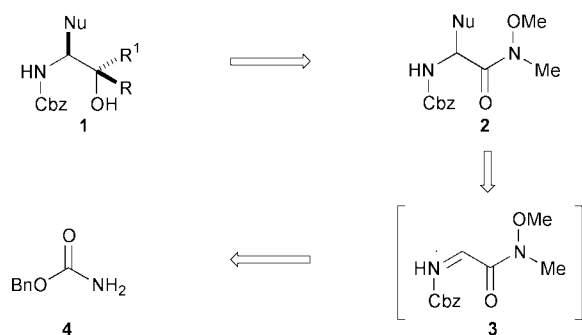
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Several substituted β -amino alcohols **1** were synthesised in a diastereoselective manner *via* the novel highly versatile intermediate **8b**, involving a combination of *N*-acyliminium ion and Weinreb amide chemistry.

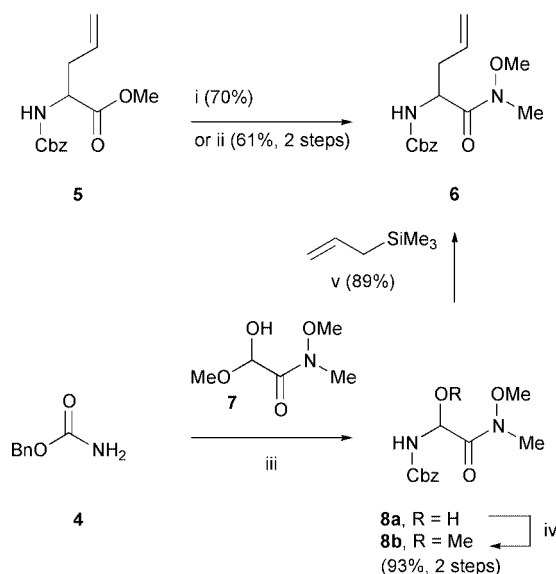
Both *N*-acyliminium ion chemistry¹ and additions of Grignard reagents to Weinreb (*N*-methoxy-*N*-methyl) amides² are widely recognised as effective tools to construct CC bonds. A large variety of π -nucleophiles can be introduced *via* addition to *N*-acyliminium ions, while a virtually infinite number of Grignard reagents can be applied to functionalise the Weinreb amide. Considering the extensive experience with *N*-acyliminium ion chemistry in our group,³ its combination with Weinreb technology would further increase its potential to form a broad range of highly functionalised molecules containing both oxygen and nitrogen. In this article, we wish to report a straightforward synthesis of β -amino alcohols **1**⁴ *via* such a combination, *i.e.* a subsequent diastereoselective, double addition of Grignard reagents to Weinreb amides **2**,^{2b,5,6} preceded by the addition of a suitable nucleophile to the *N*-acyliminium ion **3** (Scheme 1). In addition, an efficient route towards the key intermediate **2** starting from benzyl carbamate (**4**) will be discussed.



Scheme 1

In a first approach we synthesised the Weinreb amide **6** from the corresponding methyl ester **5**^{3b,7} (Scheme 2). Slight optimisation of standard conditions^{2b} to construct the Weinreb amide from methyl ester **5** (4 equiv. of AlMe_3 and $\text{MeNHOMe}\cdot\text{HCl}$ and a reaction time of 4 days) resulted in a yield of 70%. An alternative way of introducing the Weinreb amide in a two step procedure starting with hydrolysis of methyl ester **5**, followed by reaction with *N,O*-dimethylhydroxylamine using standard peptide coupling methodology, appeared to give no improvement with respect to the yield of Weinreb amide **6**.⁸

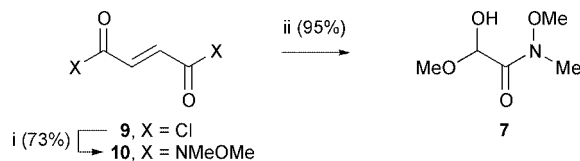
We then worked on a more elegant route involving the novel Weinreb amide **8b** which contains both precursor functionalities for *N*-acyliminium ion and Weinreb amide chemistry. Hence, *via* this species three different functionalities can be introduced (one *via* *N*-acyliminium ion chemistry and two by



Scheme 2 Reagents and conditions: (i) $\text{MeNHOMe}\cdot\text{HCl}$, AlMe_3 , CH_2Cl_2 ; (ii) 1) KOH , EtOH ; 2) diisopropylethylamine (DIPEA), 1,3-diisopropylcarbodiimide (DIPCDI), HOBT , $\text{MeNHOMe}\cdot\text{HCl}$; (iii) 4 Å MS, CH_2Cl_2 , reflux; (iv) *p*-TsOH, MeOH ; (v) $\text{BF}_3\cdot\text{OEt}_2$, CH_2Cl_2 .

organometallic additions) in three subsequent reaction steps resulting in highly functionalised compounds.

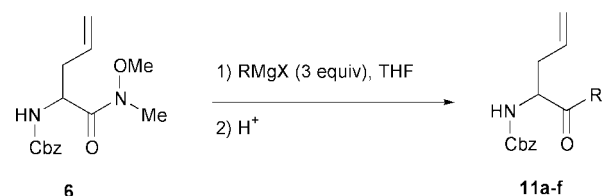
The most straightforward route to **8b** would be to condense benzyl carbamate **4** with the corresponding hemiacetal **7**, which requires an efficient synthesis of the latter species. It was found that the best way to synthesise hemiacetal **7** was to start from fumaroyl chloride (**9**, Scheme 3); double reaction of the



Scheme 3 Reagents and conditions: (i) $\text{MeNHOMe}\cdot\text{HCl}$, pyr, CH_2Cl_2 ; (ii) 1) O_3 , CH_2Cl_2 - MeOH ; 2) DMS.

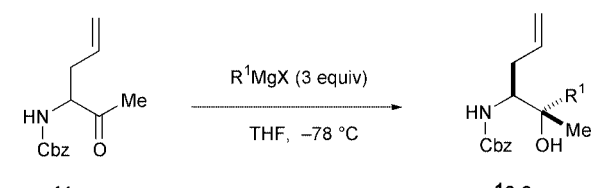
acid chloride to form the bis-Weinreb amide **10**, followed by ozonolysis in a CH_2Cl_2 - MeOH solvent mixture gave the desired hemiacetal **7** in high yield.⁹

At this point, hemiacetal **7** was coupled to benzyl carbamate and after acid-catalysed methanolysis the desired *N*-acyliminium ion precursor **8b** was obtained in virtually quantitative overall yield.¹⁰ Allyltrimethylsilane was used as the nucleophile in the Lewis acid-catalysed *N*-acyliminium ion reaction to afford homoallylic carbamate **6** in excellent yield, thus underlining the usefulness of this versatile intermediate.

Table 1 Grignard additions to Weinreb amide **6**


| Entry | RMgX | Product | yield |
|-------|-------------------|------------|------------------|
| 1 | MeMgBr | 11a | 97% |
| 2 | EtMgBr | 11b | 78% |
| 3 | AllylMgBr | 11c | 86% ^a |
| 4 | PhC≡CMgBr | 11d | 83% |
| 5 | <i>i</i> PrMgCl | 11e | 36% |
| 6 | <i>c</i> PentMgCl | 11f | 24% |

^a The corresponding isomerised α,β -unsaturated ketone was also obtained (10%).

Table 2 Grignard additions to ketone **11a**


| Entry | R ¹ MgX | Product | Yield | <i>syn</i> : <i>anti</i> ^a |
|-------|--------------------|-----------|-----------------|---------------------------------------|
| 1 | MeMgBr | 1a | 72% | — |
| 2 | EtMgBr | 1b | 82% | > 98 : 2 |
| 3 | AllylMgBr | 1c | 89% | 70 : 30 |
| 4 | PhC≡CMgBr | 1d | 9% ^b | > 98 : 2 |
| 5 | <i>i</i> PrMgCl | 1e | 23% | > 98 : 2 |
| 6 | <i>c</i> PentMgCl | — | 0% | — |

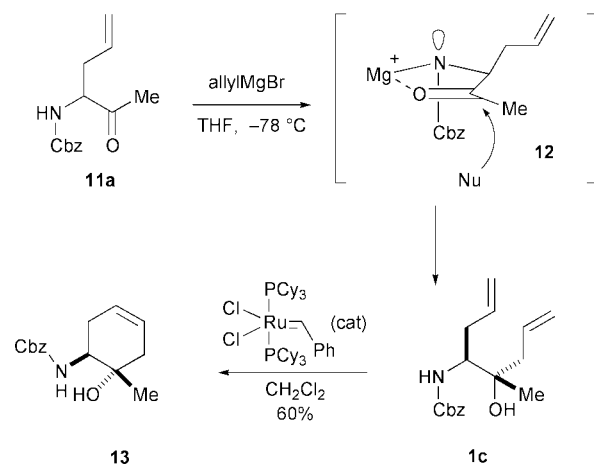
^a Ratio determined by ¹H-NMR. ^b The reaction was carried out at 80 °C; the deprotected β -amino alcohol was obtained as the main product (65%, 82 : 18 ratio of *syn* : *anti* isomers).

The Weinreb amide **6** was used as a substrate in the diastereoselective double addition of Grignard reagents to obtain β -amino alcohols. The first addition to Weinreb amide **6**^{2b,5} yielded, after acidic work-up, the corresponding protected amino ketones **11** in reasonable to high yields (Table 1). The best results were obtained by using an excess (3 equiv.) of the Grignard reagents at room temperature. With one equiv. of the Grignard reagent, the reaction does not proceed. This result demonstrates that deprotonation of the carbamate by the Grignard reagent under these conditions is faster than nucleophilic addition.¹¹

On changing from primary to secondary Grignard reagents the decreasing yields (entries 1–4 to entries 5 and 6) most likely reflect the increasing steric bulk of the organometallic reagents.

The second addition of a Grignard reagent to the methyl ketone **11a**⁶ was carried out at lower temperatures using an excess of the organometallic reagent and yielded α -amino alcohols **1** in high diastereoselectivity (Table 2). Similarly, the difference in yields between entries 1–3 and 5 and 6 can be explained by the increased steric bulk of the Grignard reagent. The low yield of amino alcohol **1d** (entry 4) can be explained by the need to use a higher reaction temperature (80 °C) in order to circumvent the initial precipitation of the Grignard reagent at lower reaction temperatures. However, at this higher temperature a side reaction resulted in the formation of 65% of the Cbz-deprotected amino alcohol (82 : 18 diastereomeric ratio).

In order to establish the configuration of the diastereoisomers and to functionalise the obtained β -amino alcohol **1c**,

**Scheme 4**

the diene was reacted in a ring-closing metathesis reaction with Grubbs' catalyst (Scheme 4).¹² After cyclisation, the configuration of the main product could be assigned as the *trans*-cyclohexene using a ¹H-NMR NOE experiment. The major isomer gave an NOE effect of 0.7% of the methyl group upon irradiation of the α -H proton, whereas in the minor isomer a 2.8% enhancement of the Me signal was observed.

The high diastereoselectivity is consistent with a chelation-controlled reaction mechanism in which magnesium most probably chelates between the nitrogen and ketone function of the starting material. In the resulting five-membered ring **12** the allyl group blocks the top face of the molecule, thus forcing the incoming nucleophile to attack from the opposite side of the ring giving rise to the *syn*- β -amino alcohol **1c** as the main product.

In conclusion, we have developed efficient syntheses of the Weinreb amide **7** and the versatile intermediate **8b**, which were successfully applied in the diastereoselective preparation of β -amino alcohols **1**. A combinatorial solid phase approach of the methodology reported herein is currently under investigation.

Acknowledgements

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References

- For a recent review, see: W. N. Speckamp and M. J. Moolenaar, *Tetrahedron*, 2000, **56**, 3817.
- (a) S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815; (b) M. P. Sibi, *Org. Prep. Proced. Int.*, 1993, **25**, 15.
- (a) H. H. Mooiweer, H. Hiemstra and W. N. Speckamp, *Tetrahedron*, 1989, **45**, 4627; (b) E. C. Roos, H. H. Mooiweer, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.*, 1992, **57**, 6769. For applications in the area of solid phase chemistry, see: (c) W. J. N. Meester, F. P. J. T. Rutjes, P. H. H. Hermkens and H. Hiemstra, *Tetrahedron Lett.*, 1999, **40**, 1601; (d) J. H. van Maarseveen, W. J. N. Meester, J. N. Veerman, C. G. Kruse, P. H. H. Hermkens, F. P. J. T. Rutjes and H. Hiemstra, *J. Chem. Soc., Perkin Trans. 1*, 2001, 994.
- For a recent review, see: S. C. Bergmeier, *Tetrahedron*, 2000, **56**, 2561.
- For a recent example of additions to amino acid-derived Weinreb amides, see, for example: M. Kratzel, R. Hiessböck and A. Bernkop-Schnürch, *J. Med. Chem.*, 1998, **41**, 2339.
- For a recent example of additions to α -keto carbamates, see, for example: M. A. Blaskovich, G. Evindar, N. G. W. Rose, S. Wilkinson, Y. Luo and G. A. Lajoie, *J. Org. Chem.*, 1998, **63**, 3631.
- U. Zoller and D. Ben-Ishai, *Tetrahedron*, 1975, **31**, 863. Using an optimised procedure for additions of hemiacetals to carbamates by R. A. T. M. van Benthem, H. Hiemstra and W. N. Speckamp, *J. Org. Chem.*, 1992, **57**, 6085.
- All compounds were obtained as analytically pure samples and adequately characterized using spectroscopic techniques (IR, ¹H- and ¹³C-NMR and HRMS).

- 9 Experimental procedure for the synthesis of hemiacetal **7**: 6.0 mL (55.5 mmol) fumaroyl chloride and 13.5 g (13.8 mmol) *N,O*-dimethylhydroxylamine HCl salt in 50 mL CH₂Cl₂ were cooled to 0 °C and 22.5 mL (278 mmol) pyridine was carefully added to the reaction mixture. The resulting dark purple reaction mixture was allowed to warm up to rt and was stirred for 18 h at this temperature. 50 mL of a saturated NH₄Cl solution was added and the layers were separated. The aqueous phase was extracted several times with CH₂Cl₂ (20 mL) until the organic phase was colorless. The combined organic layers were dried (MgSO₄), concentrated *in vacuo* and purified using flash chromatography (EtOAc–petroleum ether (PE) 50 : 50 → 100 : 0) to afford 8.29 g (41.0 mmol, 73%) of bis-Weinreb amide **10**. Data for **10**: ¹H-NMR (400 MHz, CDCl₃) δ 7.40 (s, 2H *HC=CH*), 3.66 (s, 6H, OCH₃), 3.20 (s, 6H, NCH₃). ¹³C-NMR (100 MHz, CDCl₃) δ 165.0 (CO), 130.2 (HC=CH), 61.9 (OCH₃), 32.1 (NCH₃). *v*_{max}/cm⁻¹ 2971, 1640. *m/z* (FAB) 203.1053 (M⁺ + H. C₈H₁₅N₂O₄ requires 203.1032). 4.55 g (22.5 mmol) of the bis-Weinreb amide **12** was dissolved in 75 mL CH₂Cl₂–MeOH (1 : 1) and cooled to –78 °C. O₃ was bubbled through the cold solution until the reaction mixture turned blue, then some O₂ was bubbled through until the reaction mixture turned colorless again and a large excess of S(CH₃)₂ (17 mL, 230 mmol) was added. The solution was allowed to warm up to rt and stirred for 18 h. The solvents were concentrated *in vacuo* and the resulting hemiacetal **7** (8.03 g, 42.6 mmol, 95% of a 1 : 0.5 mixture of **7** and DMSO) was used without further purification. Data for **7**: ¹H-NMR (400 MHz, CDCl₃) δ 5.18 (s, 1H, *CH*), 4.41 (br s, 1H, *OH*), 3.73 (s, 3H, NOCH₃), 3.44 (s, 3H, OCH₃), 3.21 (s, 3H, NCH₃), 2.58 (s, 6H, DMSO). ¹³C-NMR (100 MHz, CDCl₃) δ 168.8 (CO), 90.41 (*CH*), 61.5 (NOCH₃), 54.6 (OCH₃), 40.8 (DMSO), 32.3 (NCH₃). *v*_{max}/cm⁻¹ 3452, 2941, 1667.
- 10 Experimental procedure for the synthesis of Weinreb amide **8b** using hemiacetal **7**: 200 mg (1.32 mmol) benzyl carbamate and 591 mg (3.97 mmol) hemiacetal **7** in 7.5 mL CH₂Cl₂ were heated to reflux temperature. The reflux condenser was placed on top of a pressure-equalising dropping funnel filled with 4 Å MS. After refluxing for 18 h the solvent was evaporated to obtain the crude *N,O*-hemiacetal **8a**, which was dissolved in 7.5 mL MeOH. A catalytic amount (50.0 mg, 0.26 mmol) of *p*-TsOH was added, the solution was stirred for 18 h at rt and concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂, washed with a saturated NaHCO₃ solution (15 mL), a saturated NaCl solution (15 mL), dried (MgSO₄) and concentrated *in vacuo*. The crude product was purified using flash chromatography (EtOAc–PE, 50 : 50) to afford 349 mg (1.24 mmol, 94%) of **8b**. Data for **8b**: ¹H-NMR (400 MHz, CDCl₃) δ 7.34–7.26 (m, 5H, Ar-H), 6.26 (br s, 1H, *NH*), 5.77–5.74 (m, 1H, *CH*), 5.13 (s, 2H, OCH₂), 3.75 (s, 3H, NOCH₃), 3.43 (s, 3H, OCH₃), 3.19 (NCH₃). ¹³C-NMR (100 MHz, CDCl₃) δ 170.0 (CON(OMe)Me), 155.8 (OCON), 135.8, 128.3, 128.0, 127.8 (Ar-C), 85.2 (*CH*), 66.8 (OCH₂), 61.5 (NOCH₃), 55.0 (OCH₃), 31.9 (NCH₃). *v*_{max}/cm⁻¹ 3310, 3032, 2940, 1724, 1681. *m/z* (FAB) 283.1309 (M⁺ + H. C₁₃H₁₉N₂O₅ requires 283.1294).
- 11 Reaction of Weinreb amide **6** with 1 equiv. of MeMgBr for 1 h did not lead to any product formation. Upon addition of a second equiv. of EtMgBr complete formation of ethyl ketone **11b** was observed. This clearly proves that the first equiv. of the Grignard reagent is consumed by the deprotonation of the carbamate, while the second equiv. is used for the nucleophilic addition.
- 12 For a recent review, see: A. Fürstner, *Angew. Chem., Int. Ed.*, 2000, **39**, 3013.