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Optically Active Cyclopropanols by Samarium(II) Iodide Induced Intramolecular Reductive Cyclisation of β-Chloro-substituted Amides.

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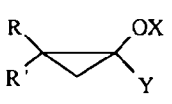
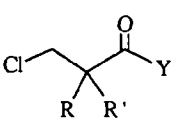
Key Words *: Chiral cyclopropanols, β-Chloro-alkyl amides. Samarium iodide, Intramolecular cyclisation.*

Abstract *: Samarium diiodide promotes under mild conditions, intramolecular reductive cyclisation of β-chloro-substituted amides, and leads with an excellent diastereomeric excess and high yield to functionalised optically active cyclopropanols.*

We have recently reported that cyclopropanone hemiketal **1a**, readily available from sodium induced cyclisation of β-halo esters **2** in the presence of Me_3SiCl, [1] underwent a one pot asymmetric Strecker synthesis to give the (*R*)- or (*S*)-2,3-methanovaline **3** (R=R'= CH_3) [2a,b] an useful herbicide. [2c] Unfortunately this cyclisation did not allow, access to the corresponding amino alcohol **1b** which in turn would constitute a more straightforward precursor of chiral methanoamino acids **3**.



1a : Y = OR
b : Y = $NR^{\bullet}$



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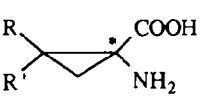
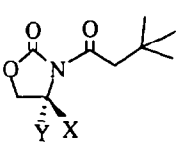


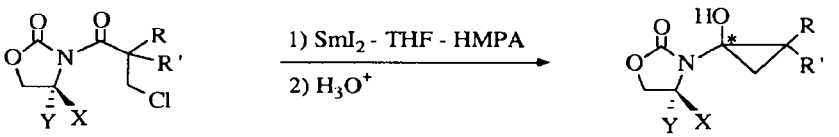
3

In order to obtain such amino alcohols **1b**, we want to test their possible formation from amide derivatives **2** (Y = oxazolidinone) by an internal SN2 reaction. Among the metals which can be used, samarium(II) iodide [3] appears the more promising. In these Barbier type processes [3d] carbanionic species seem involved. [4]

The amides used in this study were prepared as follows: **4 - 6** were obtained following the Evans' procedure [5] by N-acylation of the oxazolidinones derived from (*R*)-phenylglycinol and (*S*)-phenylalaninol. **7 - 8** were synthesised starting from the amide **4** by stereoselective enolisation with LDA in THF-HMPA [6] (-78° to -20°C), followed by alkylation with 3 equiv of chloroiodomethane (-78° to -20°C) (high yield, ds > 95%). The amide **9** was prepared by acylation of (*R*)-phenyloxazolidinone with racemic 2-*tert*-butyl-3-chloropropionyl chloride and subsequent separation of the resulting two diastereomers **8** and **9**.



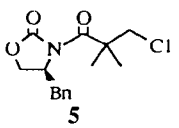
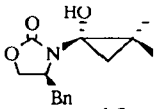
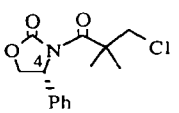
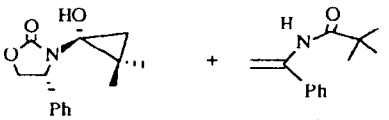
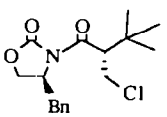
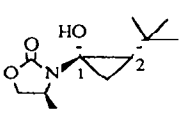
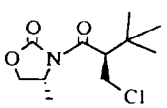
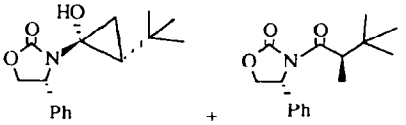
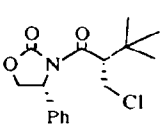
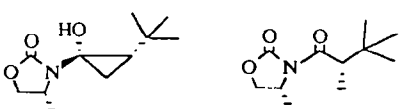
4a : X = Bn, Y = H
4b : X = H, Y = Ph



5-9 a : X = Bn, Y = H
b : X = H, Y = Ph

10-16

Table 1 Samarium(II) Iodide-promoted cyclisation of β-chloro-substituted amides **5-9**

entry	substrate	products[a]	isolated yield (%)	ds (%)
1	 **5**	 **10**	81	>95 : <5
2	 **6**	 **11** 40 : 60 **12**	92	55 : 45
3	 **7**	 **13**	95	95 : 5
4	 **8**	 **14** 77 : 23 **15**	93	95 : 5
5	 **9**	 **16** 34 : 30 **17**	62[b]	>95 : <5

[a] Stereochemistry of the major diastereomer ; [b] Starting material (36%) was recovered.

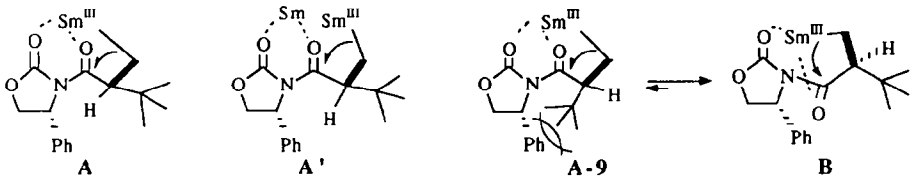
As expected we found that with SmI_2 in THF [7] in the presence of HMPA [8] the β-halo-substituted amides [9] cyclised smoothly. Optimum reaction conditions for the cyclisations involved slow addition (20 min) of a solution of the chloroalkyl amide in THF (ca : 0.05M in substrate) to 2.2 equiv of a 0.13M solution of SmI_2 containing 7 equiv of HMPA at -78°C, then warming to -20°C (1 h) and quenching at this temperature with satd. NH_4Cl solution. Reactions run in the absence of HMPA provided only low yield of the desired products, and the starting material was mainly recovered.

Thus, the intramolecular reaction of **5** under SmI_2-THF in the presence of HMPA gave exclusively the alcohol **10** in 81% yield, ($[\alpha]_D$ +38 (c 0.35, $CHCl_3$)), (Table I, entry 1). With our previous

conditions known to promote cyclisation (Na/TMSCl under sonication), [1] a large amount of the unreacted starting material and a mixture of unidentified products were obtained.

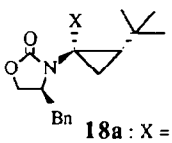
Intramolecular reductive coupling of **6** (entry 2) furnished a separable mixture of cyclopropanol **11** and enamide **12** (60%) probably formed by a competitive intramolecular hydrogen atom transfer from the C_4 position, followed by ring opening of oxazolidinone and decarboxylation. Cyclisation of **7** (entry 3) gave the cyclopropanol **13** with an excellent diastereoselectivity, over 95% ($[\alpha]_D$ +27.0 (c 1, $CHCl_3$)). The cyclisation of **8** (entry 4) led only to one diastereomer **14** ($[\alpha]_D$ -68.6 (c 1, $CHCl_3$)), accompanied by 23% of **15**, [10] formed by a ring opening reaction of **14** or by competing hydrogen atom abstraction from THF on the alkylsamarium(III) intermediate.

The amide **9**, furnished the cyclopropanol **16** in only 34% yield ($[\alpha]_D$ -133.3 (c 0.7, $CHCl_3$)), the uncyclised product **17** (30%) and unreacted starting material (36%).

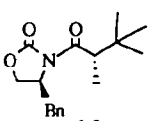


In all cyclisations induced by SmI_2-THF-HMPA, the nucleophilic species [4] probably entered the less shielded face of **A** from the side opposite to the bulky substituent of the chiral auxiliary favoured by a six-membered Sm(III) chelated ring (**A** intermediate) which provided a rigid template for subsequent cyclisation. However the complexed intermediate **A'** with two molecules of [Sm] cannot be excluded. In the case of **9**, the low yield observed in the formation of **16**, seems due to the highly disfavoured cyclisation pathway generated by the enhanced steric interactions in the intermediate **A-9**, consequently the intermediate **B** becomes more favourable.

In the products **13**, **14** and **16** we assume that the hydroxyl group is *cis* to the *tert*-butyl moiety. However we were not able to confirm (^{1}H NMR NOE difference experiments) this relative configuration. Further studies are underway.



18a : X = CN
b : X = OTMS



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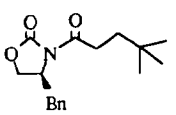

20

Several attempts were made to transform the cyclopropanol **13** into the corresponding nitrile **18a** by reaction wih KCN in acetic acid in the presence of PPh_3. Only the ring opened products **19** (45%) and **20** (55%) were obtained. In the same way, by reaction with Me_3SiCN in the presence of $SnCl_4$ the silyl alcohol **18b** (94%) was isolated.

In conclusion a SmI_2-promoted intramolecular reductive cyclisation reaction of a series of β-chloro-substituted amides has provided the corresponding cyclopropanols [11] in high yield and excellent

diastereomeric excess. Further applications of this reductive cyclisation to natural products syntheses are currently under investigation.

References and Notes

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b) Fadel, A.; Salaün, J. *Tetrahedron Lett.*, **1988**, *29*, 6257.

6) Using HMPA was necessary to increase the yield of alkylation.

7) a) The presence of trace of Sm metal in the SmI_2 solution was necessary to perform intramolecular cyclisation.
b) Very recently, when our study was finished, Molander reported the intramolecular nucleophilic acyl substitution reactions of halo-esters and lactones employing SmI_2 and $[(C_5H_{10}N)_3PO]$. Molander, G.A.; McKie, J. *J. Org. Chem.*, **1993**, *58*, 7216.

8) 3 equivalents of HMPA (vs SmI_2) were employed to prevent direct protonation and to enhance cyclisation ; see : a) Hasegawa, E.; Curran, D.P. *Tetrahedron Lett.*, **1993**, *34*, 1717.
b) Molander, G.A.; McKie, J. *J. Org. Chem.*, **1992**, *57*, 3132.

9) Piperidyl β-chloropropionic amide underwent cyclisation in the presence of Na/TMSCl, see : Wasserman, H.H.; Dion, R.P. *Tetrahedron Lett.*, **1982**, *23*, 785.

10) Unequivocal synthesis of **15** was accomplished by enantioselective alkylation, of the **4b** enolate with methyl iodide.

11) All new compounds were characterised by 250 MHz ^1H and ^{13}C NMR, IR, MS and when possible by elemental analysis (± 0.3%).
(+)-**10**. IR (neat) 1760 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.45 - 7.15 (m, 5H) ; 4.20 - 4.00 (m, 2H) ; 3.95 - 3.75 (m, H) ; 3.68 (br. s, OH) ; 3.43 (dd, J = 4.2 and 13.7 Hz, H benzyl) ; 2.85 (dd, J = 4.5 and 13.7 Hz, H benzyl) ; 1.33 (s, 3H) ; 1.12 (s, 3H) ; 0.95 (d, J = 7.3 Hz, H cycle) ; 0.71 (d, J = 7.3 Hz, H cycle). ^{13}C NMR ($CDCl_3$) δ : 157.9 (s) ; [6 arom. C : 136.0 (s), 129.2 (2d), 128.9 (2d), 127.0 (d)] ; 69.3 (t) ; 66.9 (s, C_1) ; 57.5 (d) ; 39.4 (t) ; 26.0 (s, C_2) ; 24.1 (q) ; 21.5 (q) ; 20.0 (t, C_3).

(+)-**13**. IR (neat) 1760 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.45 - 7.15 (m, 5H) ; 4.15 - 3.85 (m, 3H) ; 3.60 (dd, 3 and 13.6 Hz, H benzyl) ; 3.45 (s, OH) ; 2.77 (dd, J = 10.3 and 13.6 Hz, H benzyl) ; 1.30 - 1.00 (m, 3H cycle) ; 1.17 (s, 9H). ^{13}C NMR ($CDCl_3$) δ : 157.3 (s) ; [6 arom. C : 136.3 (s), 129.2 (2d), 128.9 (2d), 127.0 (d)] ; 66.5 (t) ; 66.4 (s, C_1) ; 57.5 (d) ; 39.3 (t) ; 35.5 (d, C_2) ; 30.0 (s, $\underline{C}$-Me_3) ; 29.6 (q, $\underline{C}H_3$) ; 18.3 (t, C_3).

(-)-**14**. IR (neat) 1755 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.40 (br, s, 5H) ; 4.91 (dd, J = 8.8 and 8 Hz, 1H) ; 4.60 (dd, J = 8 and 8 Hz, 1H) ; 4.12 (dd, J = 8.8 and 8 Hz, 1H) ; 3.19 (br, s, OH) ; 1.02 (dd, J = 10.8 and 8.0 Hz, H_a) ; 0.88 (dd, J = 6 and 8 Hz, H_b) ; 0.87 (s, 9H) ; 0.72 (dd, J = 6 and 10.76 Hz, H_c). ^{13}C NMR ($CDCl_3$) δ : 158.2 (s) ; [6 arom. C : 139.0 (d), 129.0 (2d), 128.9 (d), 127.3 (2d)] ; 70.5 (t) ; 67.4 (s, C_1) ; 59.7 (d) ; 35.6 (d, C_2) ; 29.9 (s, $\underline{C}$-Me_3) ; 29.3 (q, $\underline{C}H_3$) ; 15.6 (t, C_3).

(-)-**16**. IR (neat) 1760 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.40 (br, s, 5H) ; 5.01 (dd, J = 8.2 and 8.6 Hz, H) ; 4.61 (dd, J = 8.6 and 8.6 Hz, H) ; 4.10 (dd, J = 8.2 and 8.6 Hz, H) ; 3.31 (br, s, OH) ; 1.12 (dd, J = 11 and 5.5 Hz, H_a) ; 0.98 (dd, J = 7.6 and 5.5 Hz, H_b) ; 0.79 (s, 9H) ; 0.76 (dd, J = 11 and 7.6 Hz, H_c). ^{13}C NMR ($CDCl_3$) δ : 159.7 (s) ; [6 arom. C : 138.7 (s), 129.0 (2d), 128.9 (d), 127.7 (2d)] ; 70.5 (t) ; 67.3 (s, C_1) ; 59.6 (d) ; 34.9 (d, C_2) ; 29.6 (s, $\underline{C}$-CH_3) ; 29.1 (q, $\underline{C}H_3$) ; 15.2 (t, C_3).

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