Alkylation of Camphor and Pinanone Imines of 2-(Aminomethyl)thiazole. Enantioselective Synthesis of 2-(1-Aminoalkyl)thiazoles

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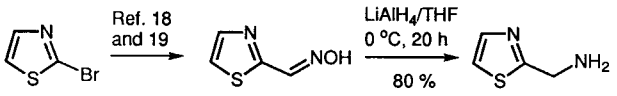
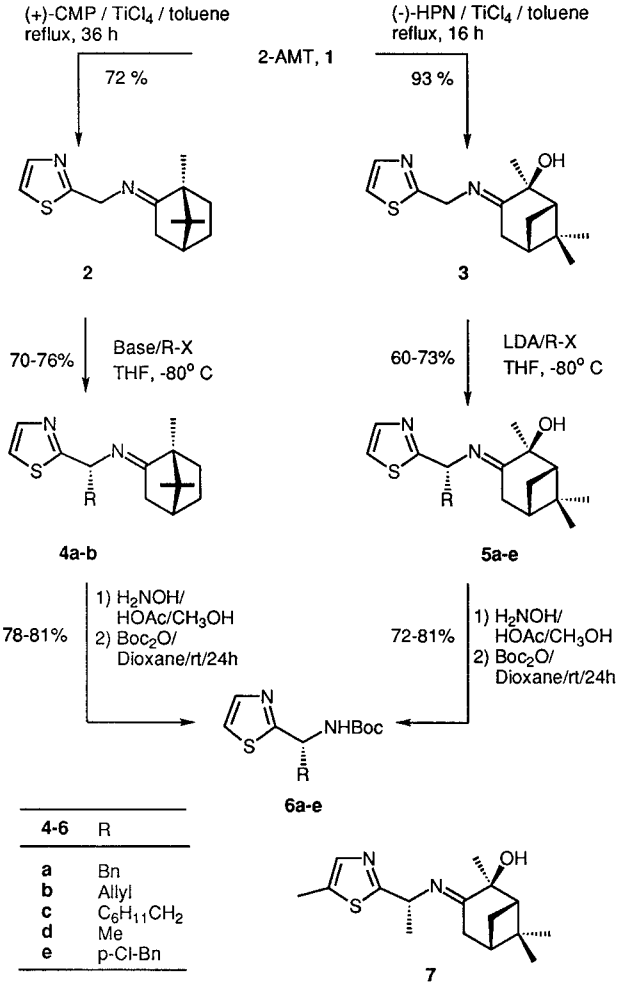
A method is described for the enantioselective synthesis of 2-(1-aminoalkyl)thiazoles **6** via stereoselective alkylation of the carbanions of (+)-(*R*)-camphor and (−)-(1*S*, 2*S*, 5*S*)-2-hydroxypinan-3-one imines **2** and **3** derived from 2-(aminomethyl)thiazole (2-AMT, **1**). Compounds **6** serve as α-amino aldehyde precursors via thiazolyl-to-formyl conversion.

The electrophilic substitution of α-amino carbanions constitutes an important topic in organic synthesis.[1] Lithio derivatives of these carbanions are currently generated by direct deprotonation of an sp^3 hydrogen α to a nitrogen atom[2] or transmetallation of α-aminoorganostannanes.[3] The latter method proved to be quite suitable for the preparation of configurationally stable derivatives.[4] Particularly interesting are α-amino carbanions stabilized by electron-withdrawing groups linked to either the anionic carbon or the nitrogen atom.[5] Carbamates[6] and formamidines[7] have been employed as stabilizing groups in several instances. Also heterocycles have been shown to provide stabilization via heteroatom–metal interaction. Thus, asymmetric alkylations of (+)-(*R*)-camphor and (−)-(1*S*,2*S*,5*S*)-2-hydroxypinan-3-one lithioketimines derived from 2-(aminomethyl)pyridine[8] and 2-(aminomethyl)furan[9] have been described. Hence we envisaged the use of thiazole in α-amino carbanion chemistry and thought that additional stabilization to the carbanion should be provided by the electron-withdrawing character of the thiazole ring.[10] Chiral aminoalkylthiazoles are of current synthetic interest since they are present in the structures of several antibiotics of marine origin such as dolastatin,[11] dysidenin,[12] isodysidenin[13] and dysideathiazoles.[14] Moreover, a useful implementation of this chemistry was also expected to arise from the synthesis of chiral α-amino aldehydes via thiazole to formyl conversion.[15]

Chiral imines of 2-(aminomethyl)thiazole (2-AMT, **1**) were considered for initial investigation. To this aim we first developed a convenient synthesis of **1** since earlier procedures involving the construction of the thiazole ring by condensation of 2-(benzoylamino)thioacetamide with chloroacetaldehyde[16] or alkylation of potassium phthalimide with 2-(chloromethyl)thiazole and conversion of the phthalimido into the amino group[17] are low yielding procedures. The recently improved synthesis of thiazole-2-carbaldehyde from 2-bromothiazole[18] and the high yielding conversion into the corresponding oxime[19] provided the basis for a new convenient synthesis of **1**. Thus, the reduction of thiazole-2-carbaldehyde oxime (2–3 g) with $LiAlH_4$ at 0 °C in THF gave **1** in 80% yield (Scheme 1). Different reaction conditions ($LiAlH_4$ in refluxing THF) or the use of other reducing agents ($NaBH_4$, BH_3–THF) induced the fragmentation of the thiazole ring or no reaction at all. Other synthetic approaches to **1** were less convenient or unsuccessful. For instance, the reductive amination of thiazole-2-carbaldehyde with cyanoborohydride in the presence of ammonia,[20] led to a 1:1 mixture of **1** and 2-(hydroxymethyl)thiazole, while attempted aminomethylation of the thiazole ring by reaction of *N*,*N*-bis(trimethylsilyl)methoxymethylamine with thiazol-2-yllithium or thiazol-2-ylmagnesium bromide[21] gave unchanged starting materials.



Scheme 1



Scheme 2

Next we considered the conversion of 2-AMT **1** to chiral imines using (+)-(*R*)-camphor [(+)-CMP] and (−)-(1*S*, 2*S*, 5*S*)-2-hydroxypinan-3-one [(−)-HPN]. In addition to the aforementioned asymmetric alkylation of heterocyclic 2-methylamines,[8,9] these chiral auxiliaries have also been used for the alkylation of alkyl glycinates.[22] Thus, the camphor and hydroxypinanone imines **2** and **3** (Scheme 2) were prepared in good to excellent yield (72% and 93%) by condensation of **1** with the corresponding ketone in refluxing toluene in the presence of $TiCl_4$. Pure compounds were isolated by filtration of crude products through a pad of silica gel and their *E* configuration was assigned by ^{1}H NMR NOE difference spectroscopy. Quite significantly, saturation of the $N-CH_2$ group signal induced a 10% enhancement of the signal corresponding to the methylene group adjacent to the imino carbon in the chiral auxiliary.

Asymmetric alkylation was initially studied with the (+)-(*R*)-camphor imine **2**. Carbanion generation by treatment of this compound with 1.0 equivalent of LDA in THF at −80 °C, followed by alkylation with benzyl bromide afforded a mixture of products in good overall yield and stereoselectivity in favor of the isomer **4a** (Table 1, entry 1). Modest effects on the stereoselectivity were observed by the change of the base stoichiometry and bulkiness (entries 2–5) and the presence of various additives such as $MgBr_2$, $ZnCl_2$ or $TiCl(i\text{-}PrO)_3$ (entries 6–8). After imine anion generation under the initially adopted conditions (LDA, THF, −80 °C), the alkylation with allyl bromide and iodomethane (entries 9 and 11) proceeded with modest or no selectivity at all and the reaction did not occur with bromomethylcyclohexane (entry 10). More satisfactory results were obtained with the hydroxypinanone imine **3** which, in fact, was alkylated more effectively by the LDA/RX system (R = benzyl, allyl, cyclohexylmethyl, 4-chlorobenzyl) to give in all cases the corresponding products **5a–c** and **5e** with excellent diastereoselectivity (ds > 98%) (entries 12–14 and 16). A somewhat lower diastereoselectivity (ds 90%) was obtained with iodomethane (entry 15). In this case, in addition to the product **5d**, the reaction produced also compound **7** (6%) arising from methylation of the thiazole. This result is not surprising when considering the acidity of H-5 of the thiazole ring[10] and the lower selectivity of iodomethane in comparison to the other electrophiles. All major stereoisomers **4a–b** and **5a–e** were isolated in good yield and fully characterized (Table 2). The *R* configuration at the newly formed stereocenter was assigned on the basis of stereochemical models similar to those employed for the alkylation of the enolates derived from glycinate imines[23] bearing the same chiral auxiliaries (+)-CMP and (−)-HPN. Further evidence for the stereochemical assignment is given below.

The removal of the chiral auxiliary from alkylimines **4a–b** and **5a–e** was carried out by treatment with hydroxylamine acetate in methanol at ambient temperature. The camphor and pinanone and oximes were recovered in 72% yield[24] and the primary amines were isolated and characterized as the *N*-Boc derivatives **6a–e** (Table 3). Products derived from either imine **2** or **3** showed identical characteristics (optical rotation), thus proving that the same stereoisomer had been obtained in both routes. Compound **6a** was characterized as the *R* enantiomer of the *N-tert*-butoxycarbonyl derivative of the natural product dolaphenine,[11] the *C*-terminal unit of dolastatin[10]. The absolute *R* configuration was also as-

Table 1. Alkylation of Imines **2** and **3**

Entry	Imine	Base (Equiv)	Additive[a]	R−X	Yield (%)[b]	ds Ratio[c]	Product [Yield (%)]
1	**2**	LDA (1.0)	none	$PhCH_2Br$	75	82 : 18	**4a** (62)
2	**2**	LDA (3.0)	none	$PhCH_2Br$	73	82 : 18	**4a** (60)
3	**2**	LDA (0.5)	none	$PhCH_2Br$	76[d]	83 : 17	**4a** (63)
4	**2**	LTMP (1.1)	none	$PhCH_2Br$	60	73 : 27	**4a** (44)
5	**2**	LHDMS (1.1)	none	$PhCH_2Br$	70	75 : 25	**4a** (62)
6	**2**	LDA (1.0)	$MgBr_2$	$PhCH_2Br$	72	80 : 20	**4a** (52)
7	**2**	LDA (1.0)	$ZnCl_2$	$PhCH_2Br$	68	82 : 18	**4a** (56)
8	**2**	LDA (1.0)	$TiCl(i\text{-}PrO)_3$	$PhCH_2Br$	63	77 : 23	**4a** (48)
9	**2**	LDA (3.0)	none	$CH_2=CHCH_2Br$	70	70 : 30	**4b** (49)
10	**2**	LDA (3.0)	none	$C_6H_{11}CH_2Br$	0[e]	–	–
11	**2**	LDA (3.0)	none	MeI	70	56 : 44	–[f]
12	**3**	LDA (3.0)	none	$PhCH_2Br$	73	> 98 : 2[g]	**5a** (72)
13	**3**	LDA (3.0)	none	$CH_2=CHCH_2Br$	65	> 98 : 2[g]	**5b** (64)
14	**3**	LDA (3.0)	none	$C_6H_{11}CH_2Br$	60	> 98 : 2[g]	**5c** (59)
15	**3**	LDA (3.0)	none	MeI	68	90 : 10	**5d** (61)
16	**3**	LDA (3.0)	none	$pClC_6H_4CH_2Br$	65	> 98 : 2[g]	**5e** (64)

[a] One equivalent.
[b] Overall yield.
[c] Determined by ^{1}H NMR on the crude reaction mixture.
[d] Determined from the unrecovered imine **2**.
[e] Only the starting imine **2** was recovered.
[f] Diastereomers were not separated.
[g] Only one diastereoisomer was detected in the ^{1}H NMR of the crude mixture.

Table 2. *N*-(Thiazol-2-ylmethyl)alkanimines **4** and **5**

Compound	Yield (%)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	^1H NMR ($CDCl_3$, 300 MHz) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$), 75.5 MHz) δ
4a	62	−6.5 (0.10)	0.60 (s, 3H), 0.82 (s, 3H), 1.02 (s, 3H), 1.22–2.38 (m, 6H), 2.42 (dt, 1H, *J* = 13.3, 2.1), 2.97 (dd, 1H, *J* = 12.9, 10.5), 3.56 (dd, 1H, *J* = 12.9, 2.8), 4.77 (dd, 1H, *J* = 10.5, 2.8), 7.18–7.25 (m, 6H), 7.75 (d, 1H, *J* = 3.2)	11.3, 18.9, 19.1, 27.1, 31.8, 35.9, 43.2, 43.7, 46.7, 54.1, 65.7, 118.7, 126.2, 128.1, 129.9, 138.6, 142.2, 175.6, 184.8
4b	49	−12.0 (0.25)	0.69 (s, 3H), 0.89 (s, 3H), 1.02 (s, 3H), 1.20–2.40 (m, 7H), 2.55 (m, 1H), 2.85 (m, 1H), 4.68 (dd, 1H, *J* = 10.3, 4.3), 5.00 (dd, 1H, *J* = 12.0, 2.5), 5.06 (dd, 1H, *J* = 17.1, 2.5), 5.76 (ddt, 1H, *J* = 17.1, 11.1, 6.8), 7.19 (d, 1H, *J* = 3.2), 7.71 (d, 1H, *J* = 3.2)	11.2, 18.9, 19.5, 27.3, 32.5, 36.2, 42.1, 43.8, 46.9, 54.2, 62.9, 117.6, 118.6, 134.6, 142.1, 175.4, 184.3
5a	72	+6.6 (4.78)	0.26 (s, 3H), 1.15 (s, 3H), 1.33 (d, 1H, *J* = 10.0), 1.42 (s, 3H), 1.87–2.05 (m, 3H), 2.16–2.20 (m, 1H), 2.44 (dd, 1H, *J* = 17.0, 3.3), 2.62 (br s, 1H, ex D_2O), 3.05 (dd, 1H, *J* = 13.0, 10.5), 3.49 (dd, 1H, *J* = 13.0, 3.1), 5.22 (dd, 1H, *J* = 10.5, 3.1), 7.18–7.21 (m, 5H), 7.24 (d, 1H, *J* = 3.2), 7.74 (d, 1H, *J* = 3.2)	22.3, 27.1, 27.8, 28.6, 33.1, 38.0, 38.1, 44.3, 45.6, 63.3, 76.6, 118.6, 126.4, 128.2, 129.7, 138.0, 142.2, 173.4, 178.0
5b	64	+8.1 (2.30)	0.89 (s, 3H), 1.31 (s, 3H), 1.46 (d, 1H, *J* = 10.0), 1.54 (s, 3H), 2.01–2.14 (m, 2H), 2.28–2.32 (m, 1H), 2.68–2.54 (m, 3H), 2.81–2.78 (m, 1H), 5.05–4.98 (m, 3H), 5.75 (ddt, 1H, *J* = 16.5, 10.4, 7.5), 7.23 (d, 1H, *J* = 3.2), 7.70 (d, 1H, *J* = 3.2)	23.1, 27.3, 27.9, 28.6, 33.7, 38.3, 38.4, 42.3, 49.8, 61.3, 77.4, 118.2, 118.6, 134.0, 142.2, 173.7, 177.7
5c	59	+9.0 (1.81)	0.88 (s, 3H), 1.31 (s, 3H), 1.45 (d, 1H, *J* = 10.0), 1.52 (s, 3H), 1.92–1.60 (m, 13H), 2.00–2.15 (m, 2H), 2.26–2.29 (m, 1H), 2.54 (br s, 1H, ex D_2O), 2.60 (d, 2H, *J* = 1.2), 5.06 (dd, 1H, *J* = 9.0, 5.1), 7.20 (d, 1H, *J* = 3.2), 7.68 (d, 1H, *J* = 3.2)	22.8, 26.4, 27.2, 27.9, 28.5, 29.6, 32.9, 33.3, 33.9, 34.4, 38.3, 45.7, 49.9, 59.3, 76.6, 118.4, 141.9, 174.3, 176.9
5d	61	+4.3 (1.01)	0.87 (s, 3H), 1.23 (s, 3H), 1.30 (d, 1H, *J* = 10.0), 1.32 (s, 3H), 1.53 (s, 3H), 2.06–2.16 (m, 2H), 2.29–2.33 (m, 1H), 2.40 (d, 1H, *J* = 3.0), 2.60–2.65 (m, 2H), 5.06 (c, 1H, *J* = 6.3), 7.22 (d, 1H, *J* = 3.2), 7.72 (d, 1H, *J* = 3.2)	22.4, 23.0, 27.3, 28.0, 28.4, 30.2, 32.8, 38.3, 50.0, 57.3, 77.7, 118.6, 139.9, 174.0, 176.3
5e	64	+13.2 (0.80)	0.33 (s, 3H), 1.19 (s, 3H), 1.33 (d, 1H, *J* = 10.0), 1.43 (s, 3H), 1.8–2.0 (m, 3H), 2.18–2.22 (m, 1H), 2.40 (dd, 1H, *J* = 17.0, 3.2), 2.60 (br s, 1H, ex D_2O), 3.05 (dd, 1H, *J* = 13.2, 9.9), 3.45 (dd, 1H, *J* = 13.2, 3.2), 5.20 (dd, 1H, *J* = 9.9, 3.2), 7.12–7.24 (m, 4H), 7.25 (d, 1H, *J* = 3.2), 7.63 (d, 1H, *J* = 3.2)	22.1, 27.1, 27.8, 28.6, 33.3, 38.0, 38.1, 43.5, 49.7, 63.1, 76.7, 118.8, 128.4, 131.2, 132.5, 135.5, 142.3, 173.0, 178.4

Table 3. 2-(1-*tert*-Butoxycarbonylaminoalkyl)thiazoles **6**

Compound	Yield[a] (%)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	$\Delta\varepsilon^{max}$ (λ nm)	^1H NMR ($CDCl_3$, 300 MHz) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$, 75.5 MHz) δ
6a	80 (78)	+24.5 (0.12)	+1.87 (227)	1.39 (s, 9H), 3.24 (dd, 1H, *J* = 13.7, 7.1), 3.3 (dd, 1H, *J* = 13.7, 6.1), 5.14 (br s, 1H), 5.27 (dd, 1H, *J* = 7.1, 6.1), m, 2H), 7.10 (m, 2H), 7.16 (d, 1H, *J* = 3.2), 7.25 (m, 3H), 7.72 (d, 1H, *J* = 3.2)	27.5, 42.1, 53.8, 80.0, 118.7, 126.7, 128.8, 129.4, 136.3, 142.5, 153.0, 171.7
6b	81 (81)	+37.2 (0.48)	+2.28 (223)	1.44 (s, 9H), 2.73 (m, 2H), 5.06–5.20 (m, 3H), 5.25 (br s, 1H), 5.72 (ddt, 1H, *J* = 17.0, 9.0, 7.0), 7.25 (d, 1H, *J* = 3.2), 7.72 (d, 1H, *J* = 3.2)	28.2, 39.9, 52.0, 80.0, 118.6, 119.7, 132.8, 142.6, 155.4, 161.8
6c	76	+23.1 (0.57)	+2.84 (223)	0.80–1.00 (m, 2H), 1.1–1.22 (m, 4H), 1.42 (s, 9H), 1.50–1.70 (m, 5H), 1.73–1.9 (m, 2H), 5.1 (m, 2H), 7.21 (d, 1H, *J* = 3.2), 7.69 (d, 1H, *J* = 3.2)	26.1, 26.3, 28.2, 32.5, 34.1, 43.6, 50.2, 79.9, 118.3, 142.5, 154.3, 163.2
6d	72	+18.3 (0.42)	+1.95 (223)	1.43 (s, 9H), 1.57 (d, 3H, *J* = 6.7), 5.20–5.23 (m, 2H), 7.40 (d, 1H, *J* = 3.2), 7.67 (d, 1H, *J* = 3.2)	21.9, 28.3, 48.5, 79.1, 118.7, 142.4, 152.7, 156.2
6e	73	+20.5 (0.2)	+2.37 (228)	1.38 (s, 9H), 2.9 (dd, 1H, *J* = 3.2, 8), 3.4 (m, 1H), 5.3 (m, 2H), 6.9–7.2 (m, 4H), 7.25 (d, 1H, *J* = 3.2), 7.72 (d, 1H, *J* = 3.2)	28.2, 42.9, 53.8, 80.1, 118.9, 127.9, 130.7, 132.7, 134.9, 142.5, 155.3, 171.3

[a] Yield from imines **5** and in parenthesis from imines **4**.

signed to **6b–e** on the basis of circular dichroism measurements showing for all compounds **6a–e** a positive Cotton effect (CE) in the region of 223–228 nm (Table 3, Figure). Recent work has shown a correlation between the sign of the CE in the range 217–230 nm and the absolute configuration at the α-center of the thiazole ring in 2-(1-aminoalkyl)thiazoles.[25,26]

Additional evidence for the stereochemical assignment and at the same time a simple illustration of the synthetic utility came from the conversion of 2-(1-*tert*-butoxycarbonylaminoalkyl)thiazoles **6a–c** into the α-amino aldehydes **8a–c** by cleavage of the thiazole ring using a well-established procedure (Scheme 3).[27] The NMR spectra of these compounds were consistent with their

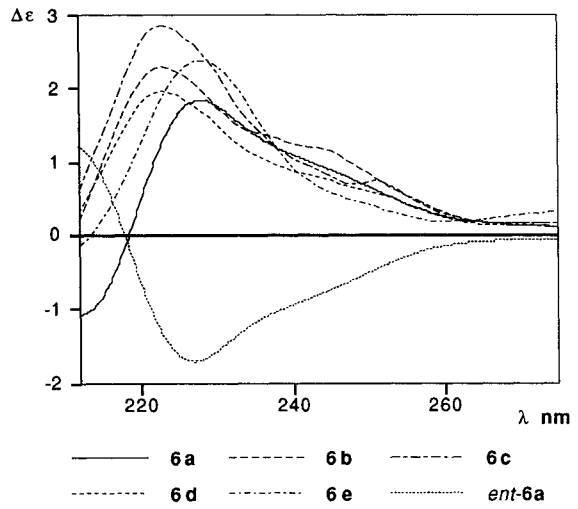


Figure. CD Spectra of 2-(1-aminoalkyl)thiazoles

structures (Table 4) and the optical rotation values of **8a** and **8c** were in agreement with the literature values.[28,29] Unfortunately, the specific optical rotation of **8b** was not available in the literature for comparison. Moreover, the enantiomeric purity of these compounds determined through the Mosher amides[30] proved to be 92% for **8b** and higher than 95% for **8a** and **8c**. Thus, due to the mild and almost neutral conditions under which the aldehydes were released from the thiazole precursors, it is very likely that their enantiomeric purity was very close, if not identical, to the degrees of diastereoselectivity in the chiral imine template alkylation step.

6, 8	R
a	Bn
b	Allyl
c	$C_6H_{11}CH_2$

Scheme 3

In conclusion, it has been shown that the stereoselective alkylation of 2-(aminomethyl)thiazole **1** can be carried out through camphor and pinanone imine derivatives **2** and **3**. The removal of the chiral inductor leads to 2-(1-aminoalkyl)thiazoles **6** in good yield and excellent enantiomeric purities. The use of either enantiomer of the chiral auxiliary in **3** indicates the possibility to synthesize compound **6** in both enantiomeric forms. Finally, owing to the thiazolyl-to-formyl equivalence, this chemistry appears to find application for the synthesis of chiral α-amino aldehydes.

Mps were determined on a Büchi 510 melting point apparatus and are uncorrected. ^{1}H- and ^{13}CNMR spectra were recorded on a Varian 300 Unity spectrometer operating at 300 MHz for ^{1}H and 75.5 MHz for ^{13}C. Chemical shifts are expressed in ppm positive values downfield from internal TMS. Coupling constants are expressed in Hz. Elemental analyses were performed on a Perkin Elmer 240B microanalyzer. Optical rotations were measured on a Perkin Elmer 241 polarimeter. CD spectra recorded in spectrograde MeOH on a JASCO J-710 dichrograph.The mass spectra were recorded on a VG AutoSpec instrument. All commercially available reagents were used as received from suppliers. All solvents were dried by the usual methods. Thiazol-2-carbaldehyde oxime was prepared as described.[19] Preparative chromatography was performed on columns of silica gel (60–240 mesh) and solvents were distilled prior to use. All new compounds gave satisfactory microanalyses: C ± 0.38 H ± 0.41 N ± 0.42.

2-(Aminomethyl)thiazole (1):
A solution of the thiazole-2-carbaldehyde oxime[19] (1.5 g, 11.7 mmol) in THF (50 mL) was treated with $LiAlH_4$ (2 g, 53 mmol) at 0 °C for 20 h. The reaction mixture was quenched with aq Na_2SO_4 (40 mL) at 0 °C and filtered. The precipitate was extracted with EtOAc (2 × 25 mL), the organic phases were dried (Na_2SO_4) and the solvent was removed at 30 °C/20 Torr to afford **1** as an oil; yield 1 g (80%); hydrochloride mp 187–189 °C (Lit.[16] mp 186 °C).

MS: *m/z* (%) = 114 (M^+, 25), 86 (100), 58 (27).

^{1}H NMR ($CDCl_3$): δ = 2.58 (br s, 2H), 4.16 (s, 2H), 7.21 (d, 1H, *J* = 3.2 Hz), 7.67 (d, 1H, *J* = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 43.7, 118.5, 142.4, 173.8.

***N*-(Thiazol-2-ylmethyl)imines; General Procedure:**
A solution of the ketone (3 mmol) in dry toluene (50 mL) was treated with 1 M $TiCl_4$ in toluene (0.9 mL, 0.9 mmol) and stirred for 5 min. Then, a solution of **1** (684 mg, 6 mmol) in dry toluene (10 mL) was added and the resulting mixture refluxed in a Dean–Stark apparatus under an argon atmosphere. The reaction was monitored by TLC and when finished (36 h for **2**, 16 h for **3**), the solvent was removed under reduced pressure and the crude product purified as detailed below.

Table 4. 2-(*tert*-Butoxycarbonylamino)alkanals **8**

Compound	Yield (%)	$[\alpha]_D^{20}$ (*c*, $CHCl_3$)	^{1}H NMR ($CDCl_3$, 300 MHz) δ, *J* (Hz)	^{13}C NMR ($CDCl_3$, 75.5 MHz) δ
8a	80	−37.2[a] (1.40)	1.49 (s, 9H), 3.08 (d, 2H, *J* = 7.0), 4.38 (q, 1H, *J* = 7.0), 5.09 (d, 1H, *J* = 7.0), 7.10–7.36 (m, 5H), 9.60 (s, 1H)	28.3, 35.6, 60.9, 80.2, 127.0, 128.8, 129.0, 135.9, 155.3, 199.1
8b	40	−27.7 (1.37)	1.50 (s, 9H), 2.49 (ddd, 1H, *J* = 12.8, 7.1, 5.7), 2.60 (ddd, 1H, *J* = 12.8, 7.0, 5.8), 4.26 (dt, 1H, *J* = 6.7, 5.7), 5.08 (br s, 1H), 5.14–5.21 (m, 2H), 5.72 (ddt, 1H, *J* = 17.8, 9.8, 7.1), 9.60 (s, 1H)	28.26, 33.6, 29.03, 80.2, 119.5, 132.0, 156.0, 199.7
8c	70	−23.9[b] (0.44)	0.90–1.00 (m, 2H), 1.01–1.30 (m, 4H), 1.41 (s, 9H), 1.52–1.71 (m, 5H), 1.73–1.90 (m, 2H), 4.21–4.32 (m, 1H), 4.81 (bd, 1H, *J* = 7.6), 9.55 (s, 1H)	26.1, 26.2, 28.2, 32.5, 33.7, 36.6, 57.7, 80.0, 155.6, 200.5

[a] **8a:** [Lit.[28] $[\alpha]_D^{20}$ + 40.4, (*S*)-enantiomer].
[b] **8c:** [Lit.[29] $[\alpha]_D^{20}$ + 26.4, (*S*)-enantiomer].

(1R,4R)-2-(Thiazol-2-ylmethylimino)bornane **(2)**; from (+)-(1*R*)-camphor (462 mg). Purified by column chromatography (hexane/Et_2O, 6:4, Et_3N, 0.5%, silica gel); yield: 556 mg (72%); oil; $[\alpha]_D^{20}$ −25.8 (c = 0.62, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 0.74 (s, 3H), 0.93 (s, 3H), 1.03 (s, 3H), 1.13–2.30 (m, 6H), 2.45 (dt, 1H, J = 2.1, 13.3 Hz), 4.72 (d, 1H, J = 17.0 Hz), 4.76 (d, 1H, J = 17.0 Hz), 7.21 (d, 1H, J = 3.2 Hz), 7.70 (d, 1H, J = 3.2 Hz).

^{13}C NMR ($CDCl_3$): δ = 11.2, 18.9, 19.6, 27.3, 31.9, 36.0, 45.8, 47.5, 53.8, 54.8, 118.6, 142.3, 175.5, 187.4.

(1S, 2S, 5S)-2-Hydroxy-3-(thiazol-2-ylmethylimino)pinane **(3)**; from (−)-(1*S*, 2*S*, 5*S*)-2-hydroxypinan-3-one (500 mg). Purified by column chromatography (hexane/Et_2O, 2:8, Et_3N, 0.5%, silica gel); yield: 737 mg (93%); oil; $[\alpha]_D^{20}$ +16.8 (c = 1.41, $CHCl_3$).

^1H NMR ($CDCl_3$): δ = 0.85 (s, 3H), 1.33 (s, 3H), 1.54 (s, 3H), 1.58 (d, 1H, J = 10 Hz), 2.02–2.13 (m, 2H), 2.32–2.42 (m, 1H), 2.54 (br s, 1H), 2.57–2.63 (m, 2H), 4.71 (d, 1H, J = 17.0 Hz), 4.80 (d, 1H, J = 17.0 Hz), 7.21 (d, 1H, J = 3.2 Hz), 7.70 (d, 1H, J = 3.2 Hz).

^{13}C NMR ($CDCl_3$): 22.8, 27.3, 28.1, 34.1, 38.2, 38.6, 42.9, 50.1, 52.5, 76.5, 118.7, 142.5, 171.9, 178.7.

Alkylation of *N*-(Thiazol-2-ylmethyl)imines 2 and 3; General Procedure:

To a solution of freshly distilled i-Pr_2NH (0.42 mL, 3 mmol) in THF (15 mL) at 0 °C and under an argon atmosphere, 1.6 M BuLi in hexanes (1.9 mL, 3 mmol) was added. The mixture was cooled to −80 °C and then a solution of imine **2** or **3** (1 mmol) and the corresponding alkyl halide (3 mmol) in THF (10 mL) was added dropwise and stirred over 1 h. The reaction was quenched with sat. aq $NaHCO_3$, extracted with Et_2O (3 × 10 mL) and the combined organic layers dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was analyzed by ^1H NMR and purified by chromatography (hexane/Et_2O, 60:50/40:50, Et_3N, 0.5%) to yield **4** or **5** (Table 2).

2-(1-*tert*-Butoxycarbonylaminoalkyl)thiazoles 6a–e; General Procedure:

To a cold solution of NaOH (25 mg, 1.1 mmol) in MeOH (50 mL), hydroxylamine hydrochloride (76 mg, 1.1 mmol) and HOAc (66 mg, 1.1 mmol) were added. After the mixture had been stirred for 5 min at 0 °C, a solution of **4** or **5** (1 mmol) in MeOH (20 mL) was added. The mixture was stirred at r.t. for 20 h, then the MeOH was removed under reduced pressure and the residue was treated with EtOAc (20 mL). The solution was washed with sat. aq $NaHCO_3$ and the solvent was removed under reduced pressure. The residue was taken up in dioxane (5 mL), Boc_2O (430 mg, 2 mmol) was added and then the solution was stirred at r.t. overnight. Evaporation of the solvent and column chromatography of the residue (hexane/Et_2O, 80:60/20:40) gave compounds **6** (Table 3). In this step, chiral inductor was also isolated as oxime derivative.

Preparation of 2-(*tert*-Butoxycarbonylamino)alkanals 8a–c; General Procedure:

A mixture of the thiazole derivative **6** (1 mmol), activated 4 Å molecular sieves (2.0 g) and MeCN (20 mL) was stirred at r.t. for 10 min. MeOTf (120 µL, 1.1 mmol) was added and the suspension was stirred for 20 min. The solvent was removed under reduced pressure. The residue was diluted with MeOH (20 mL), cooled to 0 °C and treated with $NaBH_4$ (84 mg, 2.2 mmol). The mixture was stirred at r.t. for 15 min, diluted with acetone (2 mL), filtered through Celite and concentrated in vacuo. The residue was dissolved in MeCN/H_2O (20 mL, 10:1) and then treated with CuO (240 mg, 3 mmol) and $CuCl_2 \cdot 2H_2O$ (186 mg, 1.1 mmol). The suspension was stirred at r.t. for 10 min, then filtered through Celite and concentrated in vacuo below 30 °C. The residue was partitioned between brine (30 mL) and Et_2O (30 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and passed through a plug of Florisil washing with Et_2O. The solvent was then evaporated under reduced pressure to give essentially pure the amino aldehydes **8** (Table 4).

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