DOI: 10.1002/ejoc.201100352

A Tandem Isomerization–Mannich Reaction for the Enantioselective Synthesis of β-Amino Ketones and β-Amino Alcohols with Applications as Key Intermediates for *ent*-Nikkomycins and *ent*-Funebrine

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Dedicated to Dr. Jhillu Singh Yadav on the occasion of his 60th birthday

Keywords: Natural products / Mannich reaction / Amino ketones / Amino alcohols / Allylic compounds

β-Amino ketones, with a primary amino group, are easily obtained in good yields and excellent enantioselectivities through a short sequence that involves, as a key step, a tandem isomerization–Mannich reaction from allylic alcohols with *N*-*tert*-butanesulfinimines. This method was used for the enantioselective synthesis of corresponding β-amino alcohols and also for key intermediates in the preparation of *ent*-nikkomycins or *ent*-funebrine.

Introduction

β-Amino ketones and β-amino alcohols are important key intermediates for the preparation of various types of nitrogen-containing heterocyclic compounds, as well as for the total synthesis of many bioactive molecules.[1] However, for the preparation of β-amino ketones with a primary amino group, there are only few methods available.[2] Furthermore, to the best of our knowledge, there is only one reported procedure to obtain such derivatives in optically active form; however, it involves a multistep sequence that affords low yields of the desired compounds.[3]

Several years ago we reported a new transition-metal-catalyzed tandem isomerization–aldolisation reaction starting from allylic alcohols,[4] as well as from lactols for the intramolecular process.[5] Extensive computational studies, combined with experimental data, indicated that the mechanism of this reaction was very likely to involve, in the first step, a transition-metal-catalyzed isomerization of allylic alcohols to free enols, followed by addition onto aldehydes in an "hydroxy–carbonyl–ene"-type reaction.[6] This process was successfully extended to some tandem isomerization–Mannich reactions by using *N*-protected imines as electrophiles and various catalytic systems.[7] Therefore, the next logical step was the extension of this tandem process to asymmetric synthesis and *N*-*tert*-butanesulfinyl imines appeared to be the best choice for this goal.[8] These highly versatile synthetic intermediates are easily accessible in an optically pure form[9] and, further, the chiral auxiliary can be recovered and recycled.[10]

Therefore the purpose of this publication is (1) to demonstrate that a nickel-mediated tandem isomerization–Mannich reaction from allylic alcohols with these *N*-*tert*-butanesulfinyl imines is highly efficient, affording both the *N*-protected and the free β-amino ketones with excellent yields and enantioselectivities; (2) to establish that further reductions allow the preparation of various β-amino alcohols, again in very high yields and enantioselectivities; and (3) to apply this strategy for the enantioselective synthesis of lactones *ent*-**15** and *ent*-**16**, which are key intermediates for the preparation of *ent*-nikkomycins and *ent*-funebrine, as well as their analogues.

Results and Discussion

The easily available imine **1** was selected, in the racemic form,[11] for model studies with allylic alcohol **2a**. On reaction with $[Fe(CO)_5]$ (10 mol-%) under UV irradiation, the N-protected β-amino ketones *syn*-**3a** and *anti*-**4a** were obtained in 53% overall yield with a 52:48 *syn*/*anti* ratio, together with a large amount of octane-3-one, which was the classical isomerization product of **2a**.

However, a clear improvement was observed by using our previously described catalytic system [NiHCl(dppe)]/$MgBr_2$ [dppe = 1,2-bis(diphenylphosphanyl)ethane]:[4e] a very clean reaction was obtained to afford *syn*-**3a** and *anti*-**4a** in 95%

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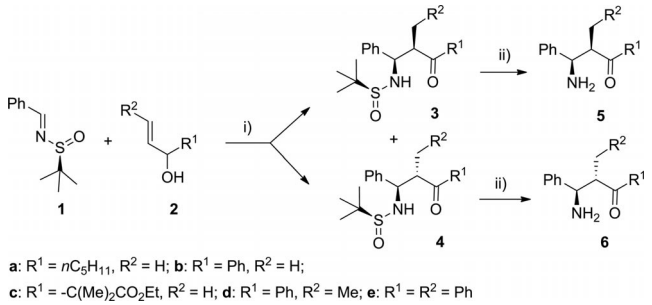
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100352.

overall yield and a ratio of 68:32. These diastereoisomers were easily separated by silica gel chromatography. Therefore, these more efficient conditions, which avoid the need for UV irradiation, were used to extend the use of this reaction to other allylic alcohols **2b**–**2e**. In all cases, the tandem reactions proved to be very efficient and afforded the desired compounds in high yields and low to moderate selectivities, except in the case of **2c** for which *anti*-**4c** was obtained as a single diastereoisomer (Scheme 1 and Table 1).



Scheme 1. Synthesis of β-amino ketones **3**–**6** by the tandem isomerization–Mannich reaction. Reagents and conditions: (i) **1** (1 equiv.), **2** (2 equiv.), [NiHCl(dppe)]/$MgBr_2$ (10 mol-%), THF –50 °C to room temp. (except for **2e**, –50 to 40 °C), 12 h, for yields and *syn*/*anti* selectivity see Table 1; (ii) 1 N aq. HCl, dioxane, room temp., 12 h, for yields see Table 1.

Table 1. Yields and selectivities for the tandem isomerization–Mannich reaction, starting from allylic alcohols **2a**–**2e** (step 1), and for the preparation of β-amino ketones **5a**–**e** and **6a**–**e** (step 2).

	Step 1[a]		Step 2[b]	
Alcohol	% Yield[c]	Ratio **3**/**4**	*syn* (% yield)	*anti* (% yield)
2a	95	68:32	**5a** (98)	**6a** (97)
2b	92	80:20	**5b** (90)	**6b** (92)
2c	82	≤ 3: ≥ 97		**6c** (84)
2d	80	62:38	**5d** (98)	**6d** (97)
2e	52	55:45	**5e** (98)	**6e** (97)

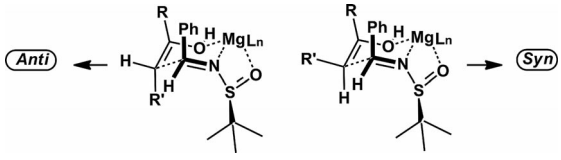
[a] Step 1 is the isomerization–Mannich reaction. [b] Step 2 is the deprotection of the amino group. [c] Overall yield.

The next step was the deprotection of the amino group. It was performed under mild acidic reaction conditions, affording efficiently the desired β-amino ketones *syn*-**5** and *anti*-**6** with a free amino group. Therefore, these derivatives were obtained in two steps only and in good to excellent overall yields from readily available starting materials.[12]

Careful analysis by NMR spectroscopy on the crude reaction mixtures demonstrated that all of these tandem reactions afforded exclusively the β-amino ketones **3** and/or **4**, establishing full stereochemical control by the chiral sulfinimine moiety. Therefore, extension to asymmetric synthesis appeared to be very attractive and we performed the same reactions starting from imine **1**, derived from (*S*)-sulfonamide, and using three representative models **2a**–**2c**.

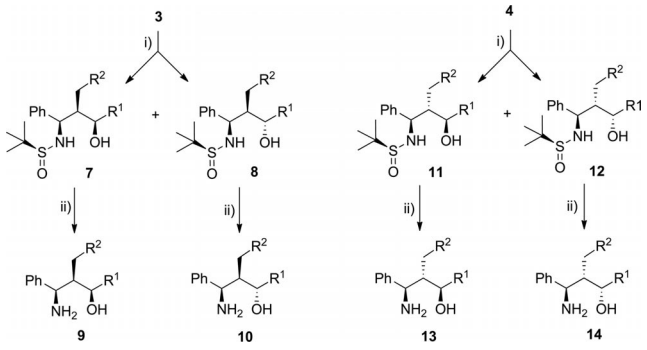
Chiral HPLC analyses of β-amino alcohols **9a**, **9b**, **10a**, **10b**, **13a**–**c**, and **14a**–**c**, obtained by the reduction of **3a**–**b** and **4a**–**c**, as described in next part (Scheme 3), gave enantiomeric excess (*ee*) values ≥99% for all of these compounds and established that the precursors **3a**, **3b**, and **4a**–**c** also have the same very high *ee* values. This was confirmed by chiral HPLC analyses performed on corresponding β-amino ketones **5a**, **5b**, and **6a**–**c**, giving again excellent *ee* values (≥99%).[13]

To propose a rationale for this high stereocontrol by the sulfinimine moiety, several factors have to be considered. The first point to notice is the role of the magnesium cocatalyst: when the reaction of **1** and **2a** was performed with [NiHCl(dppe)] only, the reaction became slower and the yield was much lower (42% instead of 95%). Based on our previous studies,[4] and literature data on additions to *N*-*tert*-butanesulfinyl imine derivatives,[8,14,15,16] we can postulate the transition states indicated in Scheme 2. Coordination of nitrogen and oxygen from sulfinylimine by the magnesium[17,18] induces a rigid system in which the nucleophile reacts exclusively from the *Re* face of the (*S*s) sulfinylimine remote from the bulky *t*Bu group.[19] On the other hand, coordination of the enol oxygen to magnesium allows classical Zimmermann–Traxler transition states to afford Mannich adducts. The *syn*/*anti* ratio is controlled by a number of factors, including the ratio of *E* and *Z* enols formed during nickel-mediated isomerization and their relative reactivity in Mannich processes. Further experimental and computational studies are required to rationalize the corresponding results in detail, however, it is worth noting that, in the case of the very bulky R substituent (**2c**), the reaction affords exclusively the *anti* isomer, which is in agreement with a reaction occurring only through the *Z* enol, due to strong R–R′ steric interactions in the corresponding *E* isomer.[20]



Scheme 2. Proposal for the transition states of the Mannich reactions.

The next step was the use of these β-amino ketones towards the preparation of optically active β-amino alcohols. The reduction of ketones **3** and **4** was performed first with $NaBH_4$ to afford, in excellent yields, the corresponding β-amino alcohols. Except for **3e** and **4e**, the stereoselectivity was very low and mixtures (close to 1:1) of the two stereoisomers **7** and **8** or **11** and **12** were obtained (Scheme 3 and Table 2). These compounds could be easily separated by chromatography and their stereochemistry was deduced from NMR spectroscopic data. Furthermore, the spectroscopic data of **9a**, **10a**, **13a**, and **14a** were fully consistent with literature.[7d] On the other hand, X-ray analyses have been performed on four derivatives: **12a**, **11c**, **7d**, and **11d** (see Figure 1 and the Supporting Information).[21] These structures not only confirmed previous assignments but also establish unambiguously that the stereochemistry at the sulfinamine level was consistent with the transition states proposed in Scheme 2 for the tandem process.



Scheme 3. Synthesis of β-amino alcohols **7**–**14**. Reagents and conditions: (i) $NaBH_4$ (1.5 equiv.), MeOH, room temp., 3 h or L-selectride (1.5 equiv.) –78 °C, THF, 3 h, yields and selectivities see Table 2; (ii) aq. HCl 1 N, dioxane, room temp., 12 h, yields see Table 2.

Table 2. Yields and selectivities for the reduction of β-amino ketones **3a**–**e**, **4a**–**e** (step 1) and for the deprotection step to β-amino alcohols **9a**–**e** and **10a**–**e**, **13e**, and **14a**–**d** (step 2).

Ketone	Step 1 $NaBH_4$ (% yield) *syn*/*anti*	Step 1 L-Selectride (% yield) *syn*/*anti*	Step 2 β-Amino alcohol (% yield)	
3a	(95) 55:45	(92) 30:70	**9a** (100)	**10a** (97)
4a	(94) 52:48	(92) 83:17	**13a** (95)	**14a** (98)
3b	(100) 54:46	(87) ≤3:≥97	**9b** (98)	**10b** (97)
4b	(100) 48:52	(92) ≤3:≥97	**13b** (100)	**14b** (97)
4c	(95) 45:55	(90) ≤3:≥97	**13c** (98)	**14c** (98)
3d	(97) 60:40	(93) ≤3:≥97	**9d** (98)	**10d** (97)
4d	(97) 45:55	(91) ≤3:≥97	**13d** (95)	**14d** (96)
3e	(98) 95:5	(89) 25:75	**9e** (98)	**10e** (97)
4e	(97) ≤3:≥97	(97) ≤3:≥97	**13e** (96)	

[a] Step 1 is the reduction of β-amino ketones. [b] Step 2 is the deprotection of amino group.

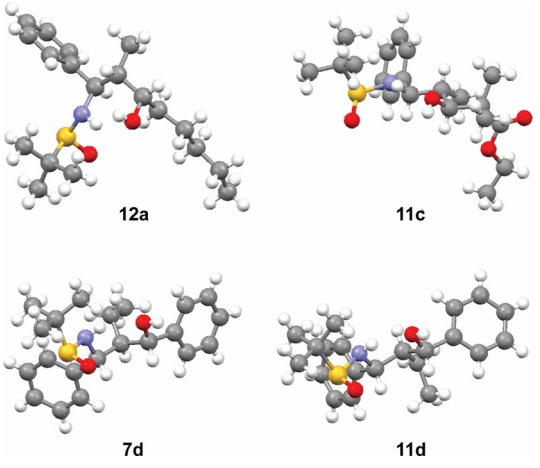
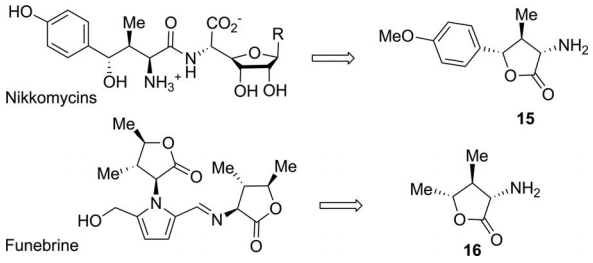


Figure 1. The molecular structures of β-amino alcohols **12a**, **11c**, **7d**, and **11d**.

Other reducing agents can be used and L-selectride was found to be more efficient, affording high to complete stereocontrol in this step. Then, the deprotection of nitrogen was performed under the same mild acidic conditions as those previously used, affording all β-amino alcohols **9**–**10** and **13**–**14** in excellent yields (Table 2).

Finally, as far as the asymmetric synthesis was concerned, chiral HPLC analyses established *ee* values ≥99% for β-amino alcohols **9a**, **9b**, **10a**, **10b**, **13a**–**c**, and **14a**–**c**. Therefore, this strategy appears to be an efficient route also for the enantioselective synthesis of such β-amino alcohols.

The stage was set for the application of these reactions to the preparation of some natural product type derivatives and we selected two α-amino lactones as targets. The first was the enantiomer of lactone **15**, which was a known key intermediate in the synthesis of nikkomycins; a family of antibiotics and antifungal compounds.[22] The second was the enantiomer of lactone **16**, which was the key component of funebrine; a compound from traditional medicine in Central America (Scheme 4).[23]

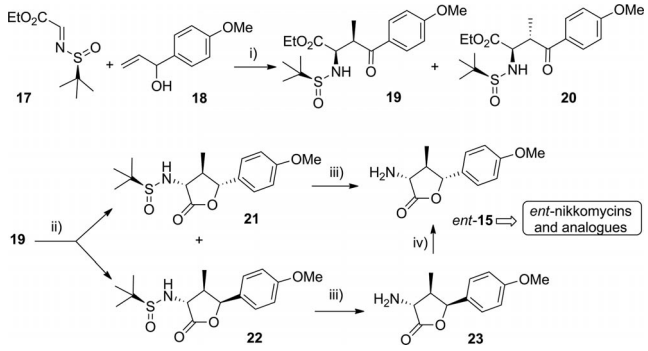


Scheme 4. Nikkomycins, funebrine, and their α-amino lactones as key components.

The condensation of easily available (*S*)-imine **17** with allylic alcohol **18**, under the previously described nickel-catalyzed conditions, afforded, in 96% yield, a mixture of the β-amino ketones **19** and **20** that were separated by chromatography. The selectivity was also very good (9:1) in favor of the desired isomer *syn*-**19**. Reduction of the latter gave the two lactones **21** and **22** in 91% overall yield in a ratio of 2:1; these lactones were easily separated by chromatography. Deprotection of **21**, under acidic conditions as previously described, afforded the desired (2*R*,3*S*,4*R*) aminolactone *ent*-**15**. The spectroscopic data of this compound were in agreement with the literature[22] and, further, the optical purity was excellent (*ee* ≥99% by chiral HPLC analyses). Therefore, this compound was obtained easily in only 3 steps and 54% overall yield from **17** (Scheme 5).

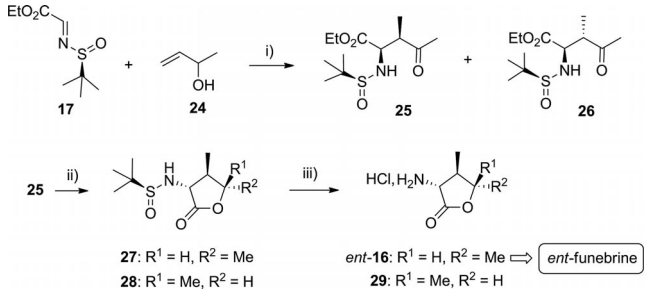
The optically active 4*S* diastereoisomer **23** was obtained in the same way from **22**, with a similar excellent *ee* value (≥99%). Furthermore, this lactone could be epimerized to *ent*-**15** by following literature procedures.[22e] Since *ent*-**15** is the enantiomer of the intermediate classically employed for the synthesis of nikkomycins,[22] it could be of use for the preparation of *ent*-nikkomycins and/or diastereoisomers of these antibiotics.

The second application was dealing with lactone *ent*-**16**. This synthesis started from the same (*S*)-sulfinyl imine **17**,



Scheme 5. Synthesis of lactone *ent*-**15**. Reagents and conditions: (i) **17** (1 equiv.), **18** (2 equiv.), [NiHCl(dppe)]/$MgBr_2$ (10 mol-%), THF –50 °C to room temp., 12 h, **19** (87% yield) and **20** (9% yield); (ii) $NaBH_4$ (1.5 equiv.), benzyl bromide (BnBr; 4 equiv.), THF, r.t. (2 h) **21** (61% yield), **22** (30% yield); (iii) aq. HCl 1 N dioxane, room temp., 12 h, *ent*-**15** (98% yield), **23** (87% yield); (iv) BBr_3 (1 equiv.), CH_2Cl_2, –78 °C (53% yield), see ref.[22e].

which was condensed with the allylic alcohol **24** to afford, in excellent yield, a 3:1 mixture of adducts **25** and **26** that were separated by silica gel chromatography (Scheme 6).



Scheme 6. Synthesis of lactones *ent*-**16** and **29**. Reagents and conditions: (i) **17** (1 equiv.), **24** (2 equiv.), [NiHCl(dppe)]/$MgBr_2$ (10 mol-%), THF –50 to 0 °C, 12 h, **25** (74% yield) and **26** (24% yield); (ii) $NaBH_4$ (1.5 equiv.), BnBr (4 equiv.), THF, room temp., 2 h, **27** (50% yield), **28** (40% yield); (iii) 1 N aq. HCl dioxane, room temp., 12 h, *ent*-**16** (98% yield), **29** (98% yield).

Reduction of major isomer **25**, under the same conditions as those described previously, afforded a 55:45 mixture of lactones **27** and **28**, which were separated by HPLC. Chiral HPLC analysis established that both compounds had *ee* values ≥99%. After deprotection of the amino groups, lactones *ent*-**16** and **29** were obtained in excellent yields as hydrochlorides. Lactone *ent*-**16** is the enantiomer of the intermediate commonly used in the synthesis of funebrine.[23] On the other hand, it is interesting to note that minor diastereoisomer **26** has the appropriate skeleton and the *anti* stereochemistry required for the synthesis of some 4-hydroxyisoleucine derivatives; another family of bioactive natural products.[24]

Conclusions

This tandem isomerization–Mannich reaction using *N*-*tert*-butanesulfinyl imines allowed a short and easy synthesis of β-amino ketones and β-amino alcohols with very high enantioselectivities, including those compounds containing primary amines. This methodology relied on easily available starting materials and used a cheap and efficient catalytic system. There was full control of the facial selectivity by the sulfinylamine moiety and this could be rationalized by coordination of the magnesium salt in the postulated transition state of this reaction, with addition on the face *anti* to the bulky *t*Bu group. Finally, it was used for short and enantiocontrolled preparations of α-aminolactones involved in the synthesis of nikkomycins and funebrine derivatives.

Experimental Section

Tandem Isomerization–Mannich Using [NiHCl(dppe)/$MgBr_2$] as the Catalyst. Synthesis of 3a and 4a as Representative Examples: A 1 M solution of $LiBHEt_3$ in THF (120 μL, 0.12 mmol) was added, under nitrogen at room temperature, to a solution of [$NiCl_2$(dppe)] (64 mg, 0.12 mmol) in anhydrous THF (6 mL). The reaction mixture was stirred for 5 min at room temperature before being transferred with a cannula into a flask containing anhydrous $MgBr_2$ (22 mg, 0.12 mmol). The reaction mixture (as a suspension) was stirred for 5 min at room temperature before being cooled to –50 °C. Then, a solution of sulfinyl imine **1** (125 mg, 0.6 mmol) in THF (1 mL) and a solution of allylic alcohol **2a** (185 μL, 1.2 mmol, 2 equiv.) in THF (1 mL) were added sequentially. The reaction mixture was allowed to warm to room temperature and kept under magnetic stirring until the starting material disappeared (TLC monitoring, usually 24 h). After addition of water (5 mL), the reaction mixture was extracted with EtOAc (3 × 5 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by chromatography on SiO_2 by using a 1:1 mixture of *n*-pentane and EtOAc as the eluent. The two diastereoisomers **3a** and **4a** were isolated as colorless solids in 95% overall yield (192 mg).

Isomer *syn*-3a: 130 mg; m.p. 112–114 °C. R_f = 0.26. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 5H, H_{Ar}), 4.60 (dd, *J* = 2.6, *J* = 5.2 Hz, 1 H, *CH*C_6H_5), 4.36 (d, *J* = 2.1 Hz, 1 H, *NH*), 2.89 (dq, *J* = 5.2, *J* = 7.1 Hz, 1 H, *CH*CH_3), 2.38–2.20 (m, 2H, CH_2CO), 1.42 (qt, *J* = 7.5 Hz, 2H, CH_2CH_2CO), 1.26–1.07 [m, 16H, (CH_3)$_3$SO, CH_3CH, (CH_2)$_2CH_3$], 0.81 (t, *J* = 7.1 Hz, 3H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7, 13.9, 22.4, 22.6, 22.9, 31.2, 42.9, 51.7, 55.7, 58.7, 127.8, 128.1, 128.4, 139.5, 214.0 ppm. HRMS: calcd. for C_7H_7NOS [M – $C_{12}H_{24}O$]$^+$ 153.02484; found 153.0247. $C_{19}H_{31}NO_2S$: calcd. C 67.61, H 9.26, N 4.15, S 9.50; found C 67.79, H 9.37, N 4.08, S 9.67. [α]$_D^{18}$ = +64.6 (*c* = 0.013, $CHCl_3$).

Isomer *anti*-4a: 62 mg; m.p. 116–118 °C. R_f = 0.32. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.32–7.23 (m, 5H, H_{Ar}), 4.63 (d, *J* = 4.2 Hz, 1 H, *NH*), 4.47 (dd, *J* = 4.2, *J* = 6.8 Hz, 1 H, *CH*C_6H_5), 2.97 (qt, *J* = 7.1 Hz, 1 H, *CH*CH_3), 2.37 (dt, *J* = 7.3, *J* = 17.1 Hz, 1 H, CH_2CO), 2.16 (dt, *J* = 7.3, *J* = 17.1 Hz, CH_2CO), 1.44 (qt, *J* = 7.2 Hz, 2H, CH_2CH_2CO), 1.27–1.08 [m, 16H, (CH_3)$_3$SO, CH_3CH, (CH_2)$_2CH_3$], 0.83 (t, *J* = 7.1 Hz, 3H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 15.4, 22.4, 22.7, 23.0, 31.2, 42.7, 52.2, 55.6, 61.5, 127.6, 127.7, 128.5, 140.5, 215.0 ppm. HRMS: calcd. for C_7H_7NOS [M – $C_{12}H_{24}O$]$^+$ 153.02484; found 153.0248. $C_{19}H_{31}NO_2S$: calcd. C 67.61, H 9.26, N 4.15, S 9.50; found C 67.91, H 9.46, N 4.10, S 9.17. [α]$_D^{18}$ = +66.0 (*c* = 0.01, $CHCl_3$).

Amino Group Deprotection Using HCl in Dioxane. Synthesis of 5a as a Representative Example: A 1 M solution of HCl (2 mL, 0.2 mmol) was added to a solution of **3a** (56 mg, 0.16 mmol) in 1,4-

dioxane (2 mL) . The reaction mixture was stirred overnight at room temperature and then extracted with pentane (3 × 5 mL) to remove byproducts. After addition of a saturated aqueous solution of $NaHCO_3$ (up to pH = 8), the reaction mixture was extracted with EtOAc (3 × 5 mL). The organic extracts were combined, dried (Na_2SO_4), and concentrated under vacuum to afford pure β-amino ketone **5a** as a colorless oil (36.5 mg, 98%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–7.17 (m, 5H, H_{Ar}), 4.16 (d, J = 6.7 Hz, 1 H, CHC_6H_5), 2.78 (qt, J = 6.9 Hz, 1 H, $CHCH_3$), 2.25 (td, J = 7.5, J = 17.1 Hz, 1 H, CH_2CO), 2.06 (td, J = 7.5, J = 17.1 Hz, 1 H, CH_2CO), 1.34 (qt, J = 7.0 Hz, 2 H, CH_2CH_2CO), 1.24–1.01 [m, 7H, CH_3CH, $(CH_2)_2CH_3$], 0.79 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1, 13.9, 22.4, 23.0, 31.2, 42.6, 53.8, 57.1, 126.7, 127.2, 127.6, 128.4, 128.5, 144.1, 214.0 ppm. HRMS: calcd. for $C_{14}H_{20}NO$ [M – CH_3]$^+$ 218.15449; found 218.1538. $[\alpha]_D^{19}$ = –66.7 (c = 0.0055, $CHCl_3$). Chiral HPLC: column, CHIRALPAK AD 250*4.6, eluent hexane/EtOH, 90:10, 1.2 mL min^{-1}, retention times for (±)-**5a**: 7.2 and 8.5 min. **5a**: retention time 7.2 min, *ee* ≥ 99%.

6a: Same procedure as that used for **5a**: Compound **4a** (87 mg, 0.26 mmol) in 1,4-dioxane (3 mL) was treated with a 1 M solution of HCl (3 mL, 0.3 mmol). Isomer *anti*-**6a** was isolated as a colorless oil (58 mg; 97%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 5H, H_{Ar}), 4.00 (d, J = 9.3 Hz, 1 H, CHC_6H_5), 2.79–2.69 (m, 1 H, $CHCH_3$), 2.53–2.30 (m, 2 H, CH_2CO), 1.62 (br. s, 2 H, NH_2) 1.51 (qt, J = 7.1 Hz, 2 H, CH_2CH_2CO), 1.26–1.17 [m, 4 H, $(CH_2)_2CH_3$], 0.81 (t, J = 7.1 Hz, 3 H, CH_2CH_3), 0.76 (d, J = 7.1 Hz, 3 H, $CHCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 15.2, 22.4, 23.1, 31.4, 42.8, 54.1, 58.8, 127.0, 127.4, 128.5, 128.6, 143.9, 215.2 ppm. HRMS: calcd. for $C_{14}H_{20}NO$ [M – CH_3]$^+$ 218.15449; found 218.1538. $[\alpha]_D^{19}$ = +57.3 (c = 0.0030, $CHCl_3$). Chiral HPLC: column, CHIRALPAK AD 250*4.6, eluent hexane/EtOH, 95:5, 1.2 mL min^{-1}, retention times for (±)-**6a**: 7.3 and 9.4 min. **6a**: retention time 7.3 min, *ee* ≥ 99%.

Reduction Using $NaBH_4$. Synthesis of 7a and 8a as Representative Examples: $NaBH_4$ (35 mg, 0.85 mmol) was added in 3 portions, under nitrogen at 0 °C, to a solution of β-amino ketone **3a** (190 mg, 0.56 mmol) in MeOH (6 mL) . The reaction mixture was kept under magnetic stirring at 0 °C until the starting material disappeared (TLC monitoring, about 1 h). After addition of water (10 mL) and extraction with EtOAc (3 × 10 mL), the organic phases were combined, washed with a saturated solution aqueous of NaCl, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by chromatography on SiO_2 by using a 1:1 mixture of *n*-pentane and EtOAc as the eluent. The two diastereoisomers **7a** and **8a** were obtained in a ratio of 55:45, as determined by ^{1}H NMR spectroscopy, and isolated in 95% overall yield (180 mg).

Isomer *syn–syn*-7a: 99 mg; m.p. 116–118 °C. R_f = 0.22. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 5 H, H_{Ar}), 5.12 (d, J = 2.1 Hz, 1 H, *NH*), 4.70 (t, J = 2.5 Hz, 1 H, *CH*C_6H_5), 4.04 (dd, J = 4.0, J = 7.8 Hz, 1 H, *CH*OH), 3.65 (br. s, 1 H, *OH*), 1.84 (ddq, J = 1.5, J = 3.0, J = 7.1 Hz, 1 H, *CH*CH_3), 1.58–1.22 [m, 17 H, $(CH_2)_4CH_3$, $(CH_3)_3SO$], 0.89 [t, J = 6.8 Hz, 3 H, $(CH_2)_4CH_3$], 0.85 (d, J = 7.1 Hz, 3 H, $CHCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 4.8, 14.0, 22.6, 22.7, 25.8, 31.8, 36.0, 44.0, 55.6, 63.3, 75.6, 127.0, 127.4, 128.1, 142.1 ppm. HRMS: calcd. for $C_{19}H_{33}NO_2NaS$ [M + Na]$^+$ 362.21297; found 362.2133. $[\alpha]_D^{18}$ = + 117.6, (c 0.0098, $CHCl_3$).

Isomer *syn–anti*-8a: 81 mg; m.p. 120–122 °C. R_f = 0.37. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.23 (m, 5 H, H_{Ar}), 4.93 (t, J = 3.5 Hz, 1 H, *CH*C_6H_5), 4.46 (d, J = 4.4 Hz, 1 H, *NH*), 3.56–3.50 (m, 1 H, *CH*OH), 3.30 (br. s, 1 H, *OH*), 1.97 (dqt, J = 3.1, J = 7.1 Hz, 1 H, *CH*CH_3), 1.69–1.31 [m, 8 H, $(CH_2)_4CH_3$), 1.28 [s, 9 H, $(CH_3)_3SO$], 0.89 [t, J = 6.6 Hz, 3 H, $(CH_2)_4CH_3$], 0.81 (d, J = 7.1 Hz, 3 H, $CHCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2, 14.1, 22.6, 22.7, 25.7, 31.9, 34.9, 44.8, 55.7, 58.6, 74.3, 126.8, 127.2, 128.1, 142.0 ppm. HRMS: calcd. for $C_{19}H_{33}NO_2NaS$ [M + Na]$^+$ 362.21297; found 362.2132. $C_{19}H_{33}NO_2S$: calcd. C 67.21, H 9.80, N 4.13, S 9.44; found C 67.34, H 9.79, N 4.03, S 9.13. $[\alpha]_D^{18}$ = +97.5 (c = 0.0011, $CHCl_3$).

Synthesis of *ent*-Nikkomycin Precursor

Step 1. Synthesis of 19 and 20: Same procedure as that used for **3a/4a**: [$NiCl_2$(dppe)] (480 mg, 0.91 mmol) in THF (15 mL); 1 M solution of $LiBHEt_3$ in THF (910 μL, 0.91 mmol); $MgBr_2$ (170 mg, 0.0.91 mmol); sulfinyl imine **17** (930 mg, 4.54 mmol) in THF (3 mL) and a solution of allylic alcohol **18** (1.49 g, 9.1 mmol) in THF (5 mL). The two diastereoisomers **19** and **20** were isolated as colorless solids in 96% yield (1.72 g).

Isomer *syn*-19: 1.55 g; m.p. 120–122 °C. R_f = 0.30. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (d, J = 8.9 Hz, 2 H, H_{Ar}), 6.93 (d, J = 8.9 Hz, 2 H, H_{Ar}), 4.34–3.95 (m, 5 H, *NH, CH*NH, *CH*CH_3, CH_2CH_3), 3.86 (s, 3 H, OCH_3), 1.35 (d, J = 7.2 Hz, 3 H, CHCH_3), 1.21 [s, 9 H, C(CH_3)$_3$], 1.19 (t, J = 6.9 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 14.8, 22.3, 43.2, 55.4, 56.5, 60.3, 61.4 113.9, 128.4, 130.7, 163.7, 171.4, 200.1 ppm. HRMS: calcd. for $C_{18}H_{27}NO_5NaS$ [M + Na]$^+$ 392.15021; found 392.1505. $[\alpha]_D^{16}$ = +55.9 (c = 0.0145, $CHCl_3$).

Isomer *anti*-20: 170 mg; m.p. 128–130 °C. R_f = 0.35. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.92 (d, J = 9.0 Hz, 2 H, H_{Ar}), 6.94 (d, J = 9.0 Hz, 2 H, H_{Ar}), 4.96 (d, J = 9.0 Hz, 1 H, *NH*), 4.16–4.06 (m, 4 H, *CH*NH, *CH*CH_3, CH_2CH_3), 3.86 (s, 3 H, OCH_3), 1.38 (d, J = 7.0 Hz, 3 H, CHCH_3), 1.26 [s, 9 H, C(CH_3)$_3$], 1.17 (t, J = 7.1 Hz, 3 H, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 15.4, 22.5, 42.0, 55.4, 56.7, 61.4, 61.8, 113.9, 128.7, 130.7, 163.8, 171.7, 201.5 ppm. HRMS: calcd. for $C_{18}H_{27}NO_5NaS$ [M + Na]$^+$ 392.15021; found 392.1504. $[\alpha]_D^{16}$ = +55.6 (c = 0.0068, $CHCl_3$).

Step 2. Synthesis of Compounds 21 and 22: $NaBH_4$ (70 mg, 1.8 mmol) was added in three portions, under nitrogen at 0 °C, to a solution of β-amino ketone **19** (328 mg, 0.89 mmol) and BnBr (0.43 mL, 3.6 mmol) in MeOH (10 mL). The reaction mixture was kept under magnetic stirring at 0 °C until the starting material disappeared (monitoring by TLC, about 1 h). After addition of water (15 mL) and extraction with EtOAc (3 × 15 mL), the organic phases were combined, washed with a saturated aqueous solution of NaCl, dried (Na_2SO_4), and concentrated under vacuum. The crude product was purified by chromatography on SiO_2 by using a 4:6 mixture of *n*-pentane and EtOAc as the eluent. The two diastereoisomers **21** and **22** were obtained in a ratio of 67:33, as determined by ^{1}H NMR spectroscopy, and isolated as colorless solids in 91% overall yield (163 mg).

Isomer *anti–anti*-21: 109 mg; m.p. 110–112 °C. R_f = 0.46. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, J = 8.7 Hz, 2 H, H_{Ar}), 6.91 (d, J = 8.7 Hz, 2 H, H_{Ar}), 4.38 (d, J = 10.0 Hz, 1 H, *CH*CO), 3.93 (dd, J = 8.0, J = 11.0 Hz, 1 H, *CH*NH), 3.82 (s, 3 H, OCH_3), 3.79 (d, J = 8.0 Hz, 1 H, *NH*), 2.34 (ddq, J = 6.4, J = 10.0, J = 11.0 Hz, 1 H, *CH*CH_3), 1.30 [s, 9 H, C(CH_3)$_3$], 1.29 (d, J = 6.4 Hz, 3 H, $CHCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3, 22.5, 47.7, 55.3, 57.0, 63.4, 84.4, 114.1, 128.1, 160.2, 174.1 ppm. HRMS: calcd. for $C_{16}H_{23}NO_4NaS$ [M + Na]$^+$ 348.1240; found 348.1241. $[\alpha]_D^{16}$ = +30.0 (c = 0.005, $CHCl_3$).

Isomer *anti–syn*-22: 54 mg; m.p. 114–116 °C. R_f = 0.43. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.06 (d, J = 8.7 Hz, 2 H, H_{Ar}), 6.92 (d, J = 8.7 Hz, 2 H, H_{Ar}), 5.55 (d, J = 8.0 Hz, 1 H, *CH*CO), 3.91 (dd, J

= 8.2, *J* = 11.0 Hz, 1 H, *CH*NH), 3.82 (s, 3 H, O*CH*$_3$), 3.71 (d, *J* = 8.2 Hz, 1 H, *NH*), 2.77 (ddq, *J* = 6.9, *J* = 8.0, *J* = 11.0 Hz, 1 H, CH*CH*$_3$), 1.29 [s, 9 H, C(*CH*$_3$)$_3$], 0.98 (d, *J* = 6.9 Hz, 3 H, CH*CH*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3, 22.5, 42.6, 55.3, 57.0, 60.2, 81.8, 114.0, 127.0, 159.7, 175.0 ppm. HRMS: calcd. for $C_{16}H_{23}NO_4NaS$ [M + Na]$^+$ 348.1240; found 348.1239. $[a]_D^{18}$ = +85.9 (*c* = 0.0058, $CHCl_3$).

Step 3. Synthesis of *ent*-15: Same procedure as that used for **5a**: compound **21** (28 mg, 0.086 mmol) in 1,4-dioxane (1.5 mL) was treated with a 1 M solution of HCl (1.5 mL, 1.5 mmol). Product *ent*-**15** was isolated as a colorless oil in 98% yield (18.6 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.7 Hz, 2 H, H_{Ar}), 6.94 (d, *J* = 8.7 Hz, 2 H, H_{Ar}), 4.80 (d, *J* = 10.1 Hz, 1 H, *CH*CO), 3.83 (s, 3 H, O*CH*$_3$), 3.41 (d, *J* = 11.6 Hz, 1 H, *CH*NH$_2$), 2.14 (ddq, *J* = 6.5, *J* = 10.1, *J* = 11.6 Hz, 1 H, *CH*CH$_3$), 1.72 (br. s, 2 H, *NH*$_2$), 1.19 (d, *J* = 6.5 Hz, 3 H, CH*CH*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 48.4, 55.3, 58.9, 84.6, 114.1, 128.0, 128.5, 160.1, 177.8 ppm. HRMS: calcd. for $C_{12}H_{15}NO_3Na$ [M + Na]$^+$ 244.09496; found 244.09490. $[a]_D^{18}$ = +28.9 (*c* = 0.0035, $CHCl_3$). Lit. values for **15**: $[a]_D^{20}$ = –32.2 (*c* = 0.57, $CHCl_3$)[22h] and $[a]_D^{19}$ = –27.3 (c 0.50, $CHCl_3$).[21f] Chiral HPLC: column: CHIRALPACK AD 250*4.6, eluent: hexane/EtOH, 85:15, 1.2 mL min^{-1}, retention times for (±)-**15**: 8.3 and 11.7 min. *ent*-**15**: retention time 11.7 min, *ee* ≥ 99%.

Step 4. Synthesis of 23: Same procedure as that used for **5a**: compound **22** (17 mg, 0.052 mmol) in 1,4-dioxane (1.0 mL) was treated with a 1 M solution of HCl (1.0 mL, 1.0 mmol). Lactone **23** was isolated as a colorless oil in 87% yield (10.1 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07 (d, *J* = 8.8 Hz, 2 H, H_{Ar}), 6.91 (d, *J* = 8.8 Hz, 2 H, H_{Ar}), 5.55 (d, *J* = 8.0 Hz, 1 H, *CH*CO), 3.83 (s, 3 H, O*CH*$_3$), 3.40 (d, *J* = 11.1 Hz, 1 H, *CH*NH$_2$), 2.55 (ddq, *J* = 6.9, *J* = 8.0, *J* = 11.1 Hz, 1 H, *CH*CH$_3$), 1.70 (br. s, 2 H, *NH*$_2$), 0.87 (d, *J* = 6.5 Hz, 3 H, CH*CH*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.9, 43.3, 55.2, 55.3, 82.0, 113.9, 127.1, 127.7, 159.5, 178.8 ppm. HRMS: calcd. for $C_{12}H_{15}NO_3Na$ [M + Na]$^+$ 244.09496; found 244.09490. $[a]_D^{18}$ = +72.8 (*c* = 0.0025, $CHCl_3$). Chiral HPLC: column: CHIRALPACK AD 250*4.6, eluent: hexane/EtOH, 85:15, 1.2 mL min^{-1}, retention times for (±)-**23**: 6.9 and 12.8 min. **23**: retention time 6.9 min, *ee* ≥ 99%.

Supporting Information (see footnote on the first page of this article): Full experimental procedures and characterization data for the tandem isomerization–Mannich synthesis of adducts **3** and **4**; deprotection to β-amino-ketones **5** and **6**; reduction to β-amino alcohols **7**, **8**, **11**, and **12**; deprotection to β-amino alcohols **9**, **10**, **13**, and **14**; and synthesis of *ent*-nikkomycin and *ent*-funebrine precursors is given.

Acknowledgments

We thank the Vietnamese Government for a Ph. D. fellowship to H. T. C. and the Centre National de la Recherche Scientifique (CNRS) and the University of Rennes 1 for financial support. We thank D. Grée for NMR spectroscopy experiments and CRMPO (Rennes) for microanalyses and MS analyses. This research has been performed as part of the Indo-French "Joint Laboratory for Sustainable Chemistry at Interfaces". We thank CNRS and the Council for Scientific and Industrial Research (CSIR) for support.

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[11] For clarity and consistency, in Scheme 1 only the derivatives with the (*S*) absolute configuration at the sulfur stereocenter are indicated because these compounds are used later in corresponding asymmetric syntheses.

[12] For another elegant asymmetric synthesis of *syn*- and *anti*-1,3-amino alcohols using metalloenamines derived from *N*-sulfinyl imines, see: T. Kochi, T. P. Tang, J. A. Ellman, *J. Am. Chem. Soc.* **2003**, *125*, 11276–11282.

[13] As expected from their structure, these β-amino ketones decompose on standing at room temperature, but their stability appears to be strongly related to the nature of R^1. Aryl ketones, such as **5b** and **6b**, are more stable, whereas alkyl derivatives are less stable. For instance, the more sensitive β-amino ketone **5a** gives a small amount of epimerization/decomposition (around 4%) during deprotection.

[14] For representative examples of allyl reagent additions to *N*-sulfinyl imines, see: a) D. A. Cogan, G. Liu, J. Ellman, *Tetrahedron* **1999**, *55*, 8883–8904; b) J. C. Gonzalez-Gomez, F. Foubelo, M. Yus, *Synlett* **2008**, *18*, 2777–2780; c) G. Kolodney, G. Sklute, S. Perrone, P. Knochel, I. Marek, *Angew. Chem.* **2007**, *119*, 9451–9454; *Angew. Chem. Int. Ed.* **2007**, *46*, 9291–9294, and references cited therein.

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[17] It is worth noting that, by adding $MgBr_2$ (1 equiv.) to imine **1**, significant downfield shifts were observed both in the ^1H NMR chemical shift of the imine proton (δ = –0.46 ppm) and in the ^{13}C NMR chemical shift of the imine carbon atom (δ = –4.4 ppm); this strongly suggests coordination of magnesium to the sulfinimine moiety.
[18] For an interesting example of a magnesium salt coordinated to a –N–S=O unit, see: J. K. Brash, T. Chivers, M. Parvez, G. P. A. Yap, *Inorg. Chem.* **1999**, *38*, 3594–3595.
[19] Based on literature data,[8] in an open transition state, addition should occur on the *Si* face of our (S_s) sulfinimine to afford the other stereoisomer, which is not consistent with our experimental results.
[20] Reactions via the *cis* isomer of the sulfinyl imine have been proposed to explain the stereoselectivity during reactions with cyclohexadienyl Grignard reagents, see: M. S. Maji, R. Fröhlich, A. Studer, *Org. Lett.* **2008**, *10*, 1847–1850; however, to the best of our knowledge, there is no evidence to date for a possible *trans–cis* isomerization with these *N*-*tert*-butanesulfinyl imines.
[21] CCDC-802575 (for **12a**), -802578 (for **11c**), -802576 (for **7d**), and -802577 (for **11d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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Received: March 12, 2011
Published Online: May 17, 2011

