An Efficient Enantioselective Synthesis of Strigolactones with a Palladium-Catalyzed Asymmetric Coupling as the Key Step

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An efficient enantioselective methodology for the preparation of the strigolactones GR7, GR24 and Nijmegen-1 based on palladium-catalyzed asymmetric coupling has been developed. The products are obtained in good yield and high optical purity. This methodology is an attractive alternative for installing the stereochemistry at C2′ of the D-ring.

Introduction

Parasitic weeds belonging to the genera *Striga* and *Orobanche* severely reduce yields of economically important crops in tropical areas of the eastern hemisphere.[1] Important food crops such as maize, sorghum, millet and rice are host plants that can suffer enormously from these parasitic weeds, leading to considerable losses in crop yield, in some cases more than 50%. The parasitic process begins with the germination of the weed seeds, which is induced by a stimulant present in the root exudates of the host plant. Several naturally occurring germination stimulants, namely (+)-strigol[2] (Figure 1), (+)-sorgolactone,[3] (+)-orobanchol[4] and alectrol[5] have been isolated from host and nonhost plants. Structure-activity studies of the natural stimulants[6–9] and of their synthetic analogues GR7,[10] GR24[11] and Nijmegen-1[12] (Figure 1) have revealed that the absolute configuration at the stereogenic centers of the stimulant is of great importance for the germination activity. For instance, the optical antipode of (+)-strigol has to be 500 times more concentrated to be as active as the natural isomer in the seeds of *Striga asiatica*.[6] It may therefore be concluded that germination stimulants are recognized in a highly selective manner by the parasitic seeds. The synthesis of strigol-type compounds is interesting for several reasons: i) to gain insight into the structure-activity relationships of these semiochemicals, ii) to provide the chemical basis for studying the biochemistry of the recognition and germination processes, and iii) to develop new methods for parasitic weed control.[14]

Several synthetic strigol analogous, commonly called strigolactones, have germination activity as high as the natural stimulants. The synthetic stimulant GR24 (**3**) is a very potent synthetic germination stimulant,[13] which is used worldwide in parasitic weed research to stimulate germination and is a standard for comparing the activity of new germinating agents. Nijmegen-1[12] (**4**) is an attractive stimulant for *Striga* control by the suicidal germination approach.[14]

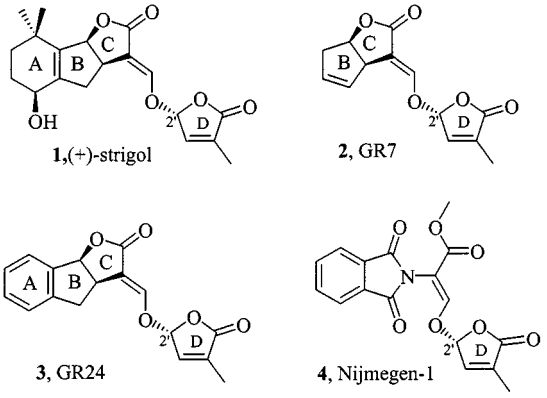

Figure 1. Structures of strigolactones

Over the years extensive efforts have been made to prepare natural and synthetic stimulants in an enantiopure form. The basic strategies reported hitherto for the synthesis of stereohomogenous strigolactones are: i) resolution of the racemic stimulant at the final stage by covalent coupling with a suitable resolving agent[15] or by chromatography on a chiral column,[6,9,16] ii) coupling of the enantiopure ABC fragment[10a,17–19] with the racemic D-ring precursor and subsequent chromatographic separation of the thus-obtained diastereomeric mixture, iii) coupling of the racemic ABC fragment with an enantiopure D-ring precursor[10b,20,24] and subsequent separation of the resulting diastereomers, and iv) by using starting materials from the chiral pool for the synthesis of an enantiopure ABC fragment.[21–23] Note that the B and C rings in strigolac-

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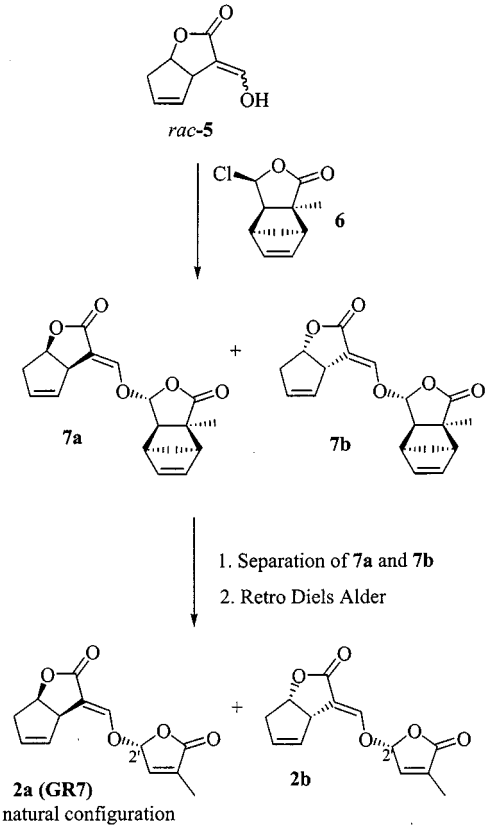
tones always have a *cis* relationship, because the *trans* structures are too highly strained.

A methodology of type *iii* developed earlier by us involves control of the stereochemistry at C2′ with the enantiopure D-ring synthon **6**[24] (Scheme 1). It should be emphasized that the absolute configuration at C2′ is essential for biological activity. Our methodology was successfully applied in the preparation of all eight stereoisomers of sorgolactone[8] as well as the synthetic stimulants GR7,[10b] GR24,[11] Nijmegen-1[12] and desmethylsorgolactone[25] in enantiopure form. Welzel et al. installed the correct stereochemistry at C2′ in a highly selective manner by using Winterfeldt's template as a chiral auxiliary.[26] Even though the products were obtained in high enantiopurity, preparation of the homochiral D-ring **6** or Welzel's D-ring precursor requires considerable synthetic effort. Furthermore, during the removal of the auxiliary in the final step considerable loss of material had to be accepted, resulting in yields of 50% at best.

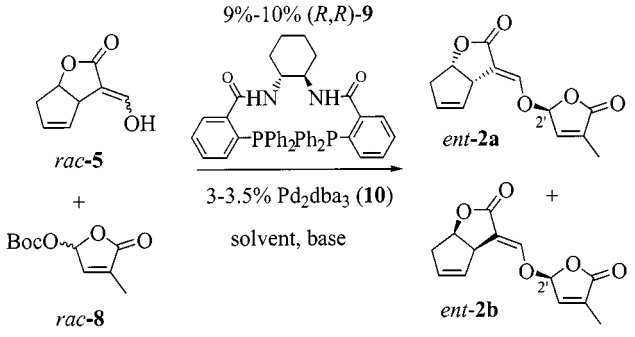


Scheme 1. Synthesis of **2a** and **2b**

We envisaged that asymmetric coupling of a D-ring synthon with the racemic ABC fragment would provide an attractive alternative to the existing strategies for the synthesis of enantiopure strigolactones. For this purpose the palladium-mediated coupling method developed by Trost for the synthesis of (−)-Aflatoxin B Lactone[27] would be a conceivable approach for the asymmetric strigolactone synthesis. In this paper we report the results of such asymmetric coupling reactions of the D-ring to the racemic ABC part for the synthesis of the stimulants GR7, GR24 and Nijmegen-1.

Results and Discussions

The coupling of the ABC fragment involves the reaction of an enol with a D-ring precursor, containing a suitable leaving group at C-5, as the electrophile. Palladium-catalyzed *O*-alkylation of enols has no precedent in the literature. Initial attempts were carried out with the racemic enol **5**[10] which constitutes the ABC part of the stimulant GR7. Coupling of the racemic D-ring precursor **8**,[28] containing an OBoc as the leaving group, with the achiral ligand 1,2-bis(diphenylphosphanyl)ethane (9%) in the presence of Pd_2dba_3 (3%) **10** in THF at room temperature resulted in a mixture of racemic coupling products *rac*-**2a** and *rac*-**2b** in a ratio of 1:1.5 in a 90% yield after 1 hour. These diastereomers could be readily separated by column chromatography (silica gel, hexane/ethyl acetate). Having demonstrated the feasibility of the Pd-mediated coupling, the use of a chiral ligand [the Trost ligand (*R*,*R*)-**9**[29]] in the presence of Pd_2dba_3 was considered next (Scheme 2). Under similar conditions, a mixture of *ent*-**2a** and *ent*-**2b** with enantiopurities of 78% and 86%, respectively, was obtained in 90% yield (Table 1, entry 1). Addition of a tertiary amine base (Et_3N) to facilitate the nucleophilic reaction of the enol had no significant effect on the enantioselectivity (entry 2). Changing the solvent from THF to CH_2Cl_2, still with Et_3N as the base, improved the *ee* of the coupling products to 88% and 92%, respectively (entry 3). Lowering the temperature resulted in excellent *ee*'s of 96% and 98%, respectively (entry 4). The absolute configuration at C2′ of *ent*-**2a** and *ent*-**2b** was assigned as *S* by comparing the optical rotations of both coupling products with those reported previously.[10] The resulting stereochemistry at C2′ is opposite to that of the naturally occurring stimulant strigol. In order to obtain the diastereomers with the natural configuration at C2′, the ligand (*S*,*S*)-**9** was used, which resulted in the expected diastereomers of GR7 with high *ee*'s (entries 5 and 6).



Scheme 2. Synthesis of *ent*-**2a** and *ent*-**2b**

Since all possible stereoisomers of stimulant GR7 were obtained by using the Pd-catalyzed coupling, the methodology was next extended to the preparation of the four dia-

Table 1. Asymmetric coupling of *rac*-**5** with *rac*-**8**

Entry[a]	Solvent/base	Ligand	Absolute configuration at C2′[b]	Yield[c] (%)	Product (*ee*)[d]	
1	THF	(*R*,*R*)-**9**	*S*	90	*ent*-**2a** (78)	*ent*-**2b** (86)
2	THF/Et_3N	(*R*,*R*)-**9**	*S*	89	*ent*-**2a** (75)	*ent*-**2b** (84)
3	CH_2Cl_2/Et_3N	(*R*,*R*)-**9**	*S*	74	*ent*-**2a** (88)	*ent*-**2b** (92)
4[e]	CH_2Cl_2/Et_3N	(*R*,*R*)-**9**	*S*	67	*ent*-**2a** (96)	*ent*-**2b** (98)
5	CH_2Cl_2/Et_3N	(*S*,*S*)-**9**	*R*	88	**2a** (90)	**2b** (98)
6[e]	CH_2Cl_2/Et_3N	(*S*,*S*)-**9**	*R*	75	**2a** (93)	**2b** (94)

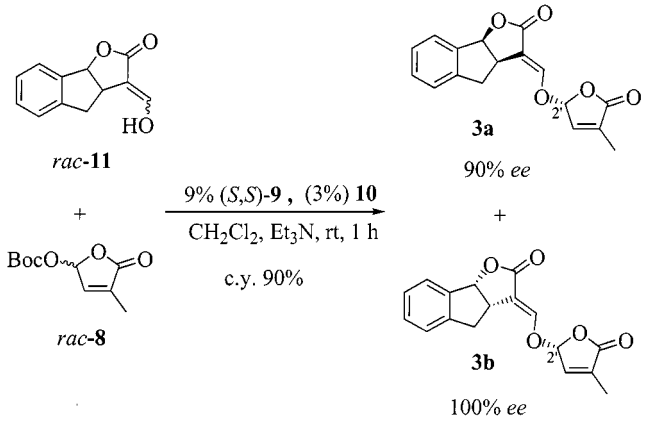
[a] Unless stated otherwise all reactions were carried out at room temperature, with 3.0−3.5% $Pd_2(dba)_3$/$CHCl_3$ and 9−10% ligand (*R*,*R*)-**9** or (*S*,*S*)-**9**. The ratio of **5**, **8** and triethylamine was 1:2:1. [b] The absolute configurations were determined by comparison of their rotation with those reported previously.[10] [c] Combined yield of **2a** and **2b,** or of *ent*-**2a** and *ent*-**2b**. The diastereomeric ratio is 1:1.5 in both cases. [d] Determined by HPLC on a Chiralcel OD column with hexane/EtOH or hexane/2-propanol, 1 mL/min, 254 nm. [e] The temperature employed was −10 °C to room temperature.

stereomers of stimulant GR24 (**3**) and both enantiomers of Nijmegen-1 (**4**) (Table 2, Scheme 3 and 4). Under the conditions indicated in Scheme 3, the enol of racemic lactone **11**[11] was coupled to give stereoisomers **3a** and **3b** when chiral ligand (*S*,*S*)-**9** was used (Scheme 3). The enantiopurities of **3a** and **3b** were determined as 90% and 100%, respectively. Lowering the temperature or the catalyst loading of Pd_2dba_3 to 2% did not improve this optical yield. However, crystallization improved the enantiopurities of **3a** and **3b** from an initial 88% and 93% to the above-mentioned 90% and 100%, respectively. When the antipodal catalyst (*R*,*R*)-**9** was used *ent*-**3a** and *ent*-**3b** were similarly obtained in high optical yields (Table 2, entry 2).

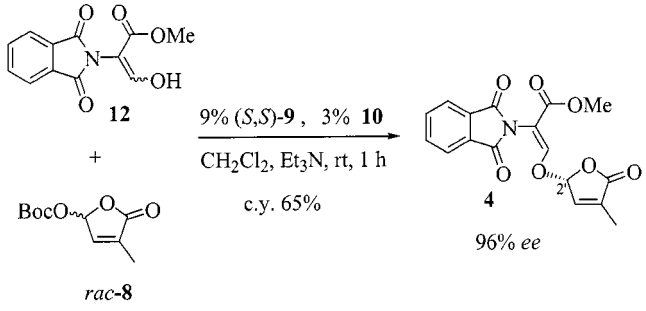
Table 2. Asymmetric coupling of *rac*-**11** and **12** with *rac*-**8**[a]

Entry	Enol	Ligand	Absolute configuration at C2′[b]	Yield (%)	Products (*ee*%)[c]
1	**11**	(*S*,*S*)-**9**	*R*	90[d]	**3a** (90)[e] **3b** (100)[e]
2	**11**	(*R*,*R*)-**9**	*S*	85[d]	*ent*-**3a** (94) *ent*-**3b** (100)
3	**12**	(*S*,*S*)-**9**	*R*	65	**4** (96)
4	**12**	(*R*,*R*)-**9**	*S*	60	*ent*-**4** (97)

[a] All reactions were carried out at room temperature in dichloromethane as the solvent, with 3.0% $Pd_2(dba)_3CHCl_3$ and 9% (*R*,*R*)-**9** or (*S*,*S*)-**9**. The ratio of **11** or **12**, **8** and Et_3N was 1:2:1. [b] The absolute configurations were determined by comparison of their rotation with the previously reported values.[11,12] [c] Determined by HPLC on Chiralcel-OD® column with hexane/EtOH mixtures. [d] Combined yield of both diastereomers obtained in a ratio of 1:1.4. [e] After recrystallization from hexane/ethyl acetate mixture.



Scheme 3. Synthesis of **3a** and **3b**



Scheme 4. Synthesis of **4**

Coupling of **12**,[12] which is the basic fragment of Nijmegen-1, favored the enantiomer with the natural configuration at C2′ when (*S*,*S*)-**9** was used as the chiral catalyst, while the antipode *ent*-**4** was obtained by employing (*R*,*R*)-**9** as the ligand in the Pd-catalyzed coupling (Table 2, entry 3 and 4).

In conclusion, we have developed a short and efficient methodology for the asymmetric synthesis of all possible stereoisomers of the strigolactones GR7, GR24 and Nijmegen-1. The key step is the palladium-catalyzed asymmetric coupling of lactones **5**, **11**, and **12**, with the D-ring precursor *rac*-**8**. This methodology is an attractive alternative to the existing routes, which in most cases are more laborious and result in lower yields. The essential feature of the asymmetric coupling is that the D-ring precursor reacts with palladated chiral ligand to give a chiral electrophilic species. The BocO group is a suitable C-5 substituent in butenolide **8**. On the basis of the successful coupling in the synthesis of three stimulants, it may be expected that this methodology can be extended to practically any synthesis of a strigolactone, including the naturally occurring ones.

Experimental Section

General: The lactones *rac*-**5**,[10] *rac*-**11**,[11] and **12**[12] were prepared according to the procedure described in the literature. All reagents were obtained commercially and were used without purification. All reactions were carried out under an inert atmosphere (argon). Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Triethylamine was distilled from KOH and stored over molecular sieves. Column chromatography was carried out on Merck silica gel 60 (60−75 mesh) with hexane/ethyl acetate mixtures. All enantiomeric purities were determined by using the column Chiralcel-OD®, 4.6 mm × 25 cm; solvent: hexane/EtOH or hexane/2-propanol, flow rate: 1 mL/min; detector: 254 nm; temperature: room temperature.

General Procedure for the Coupling: CH_2Cl_2 (1 mL, dry and oxygen free) was added to a test tube containing *rac*-**8** (55 mg, 0.257 mmol), **10** (4.1 mg, 0.004 mmol) and the ligand (*S*,*S*)-**9** (8.3 mg, 0.012 mmol). The resulting purple mixture was stirred for 20 min, giving a clear yellow solution. The yellow reaction mixture was then treated with Et_3N (13.1 mg, 0.129 mmol) and **12** (32 mg, 0.129 mmol,) and subsequently stirred at room temperature until TLC (hexane/EtOAc 1:1) showed no remaining starting material (1 h). The yellow reaction mixture was then absorbed on silica and chromatographed (hexane/ethyl acetate, 1:1) to afford the product as a colorless solid (28.8 mg, 65% yield). The enantiomeric purity of the product was determined on a Chiralcel-OD® column, solvent: hexane/EtOH, flow rate: 1 mL/min.

***ent*-2a and *ent*-2b:** CH_2Cl_2 (1 mL, dry and oxygen free) was added to a test tube containing *rac*-**8** (35 mg, 0.160 mmol), **10** (3 mg, 0.003 mmol) and the ligand (*R*,*R*)-**9** (6 mg, 0.009 mmol). The resulting purple mixture was stirred for 30 min at −10 °C, giving a clear yellow solution. Et_3N (12 μL, 0.086 mmol) and *rac*-**5** (13 mg, 0.086 mmol) were then added to this reaction mixture, which was allowed to warm to room temperature. Once TLC (hexane/EtOAc, 1:1) showed no trace of starting material (3 h), the crude mixture was absorbed on silica and chromatographed (hexane/ethyl acetate, 1:1) to afford the products as a white solid (14.2 mg, 67%). The diastereomeric ratio of *ent*-**2a** and *ent*-**2b** was 1:1.5 (see Table 1,entry 4).

***ent*-2a:** $[\alpha]_D^{22} = -330$ ($c = 1.00$, CH_2Cl_2) {ref.[10] $[\alpha]_D = -341$ ($c = 1.03$, CH_2Cl_2)}. Chiral HPLC analysis; OD column (hexane/2-propanol, 6:4, 1 mL/min): $t_R = 8.5$ min (2%) and 9.6 min (95%.) The enantiomeric purity of *ent*-**2a** was estimated to be 96%.

***ent*-2b:** $[\alpha]_D^{22} = -165$ ($c = 1.03$, CH_2Cl_2) {ref.[10] $[\alpha]_D = -179$ ($c = 1.44$, CH_2Cl_2)}. Chiral HPLC analysis; OD column (hexane/EtOH, 8:2, 1 mL/min), $t_R = 9.3$ (95%) and 11.1 min (1%). The enantiomeric purity of *ent*-**2b** was estimated to be 98%.

Their spectroscopic data (^{1}HNMR, ^{13}C NMR and IR) were in full agreement with those reported in ref.[10]

Compounds 2a and 2b: Obtained as described for *ent*-**2a** and *ent*-**2b**, but with (*S*,*S*)-**9**. Starting from *rac*-**8** (35 mg, 0.160 mmol) and ligand (*S*,*S*)-**9** (6 mg, 0.009 mmol), the reaction was complete after 1 h. Purification by chromatography (SiO_2, hexane/ethyl acetate, 1:1) gave the products (15.9 mg, 75% yield) in a diastereomeric ratio of 1:1.5 (see Table 1, entry 6).

2a: $[\alpha]_D^{22} = +320$ ($c = 1.1$, CH_2Cl_2) {ref.[10] $[\alpha]_D$ +339 ($c = 1.06$, CH_2Cl_2)}. Chiral HPLC analysis; OD column (hexane/EtOH, 8:2, 1 mL/min), $t_R = 11.5$ min (5%) and 12.5 min (95%). The enantiomeric purity of **2a** was estimated to be 90%.

2b: $[\alpha]_D^{22} = +165$ ($c = 1.40$, CH_2Cl_2) {ref.[10] $[\alpha]_D = +174$ ($c = 1.44$, CH_2Cl_2)}. Chiral HPLC analysis; OD column, $t_R = 9.26$ min (3.6%) and 11.0 min (95%). The enantiomeric purity of **2b** was estimated to be 93%. (see Table 1, entry 5)

Their spectroscopic data (^{1}HNMR, ^{13}C NMR and IR) were in full agreement with those reported in ref.[10]

Compounds 3a and 3b: These compounds were synthesized according to the general procedure starting from *rac*-**11** (33 mg, 0.163 mmol) and (*S*,*S*)-**9**. The reaction was complete after 1 h. Purification by chromatography (SiO_2, hexane/ethyl acetate 1:1) gave the products as a white solid (48.6 mg, 90%). The diastereomeric ratio was 1:1.4 (see Table 2,entry 1). Their spectroscopic data (^{1}H NMR, ^{13}C NMR and IR) were in full agreement with those reported in ref.[11]

3a: $[\alpha]_D^{22} = +420$ ($c = 0.2$, $CHCl_3$) {ref.[11] $[\alpha]_D = +436$ ($c = 0.25$, $CHCl_3$)}. Chiral HPLC analysis; OD column (7:3−8:2 gradient hexane/EtOH, 1 mL/min), $t_R = 10.6$ min (3%) and 12.8 min (93.4%). The enantiomeric purity of **3a** was estimated to be 90% after a single crystallization (hexane/ethyl acetate).

3b: $[\alpha]_D^{22} = -274$ ($c = 0.2$, $CHCl_3$) {ref.[11] $[\alpha]_D = -272$ ($c = 0.2$, $CHCl_3$)}. Chiral HPLC analysis; OD column (hexane/EtOH, 7:3, 1 mL/min), $t_R = 9.3$ min (not detected by the HPLC) and 11.4 (100%) min. The enantiomeric purity of **3b** was estimated to be 100% (see Table 2,entry 1).

Compounds *ent*-3a and *ent*-3b: These compounds were synthesized according to the general procedure starting from *rac*-**11** (49 mg, 0.242 mmol) and (*R*,*R*)-**9**. The reaction was complete after 1.0 h. Purification by chromatography (SiO_2, hexane/ethyl acetate, 1:1) gave the products as a white solid (61.4 mg, 85%). The diastereomeric ratio was 1:1.4 (see Table 2, entry 2).

***ent*-3a:** $[\alpha]_D^{22} = -436$ ($c = 0.25$, $CHCl_3$) {ref.[11] $[\alpha]_D = -446$ ($c = 0.25$, $CHCl_3$)}. Chiral HPLC analysis; OD column (hexane/EtOH, 7:3, 1 mL/min), $t_R = 10.3$ min (94.7%) and 12.06 min (3%). The enantiomeric purity of *ent*-**3a** was estimated to be 94%.

***ent*-3b:** $[\alpha]_D^{22} = +270$ ($c = 0.2$, $CHCl_3$) {ref.[11]$[\alpha]_D = +273$ ($c = 0.2$, $CHCl_3$)}. Chiral HPLC analysis; OD column (7:3 hexane/EtOH, 1 mL/min) $t_R = 8.72$ (100%) and 10.1 min (not detected by the HPLC). The enantiomeric purity of *ent*-**3b** was estimated to be 100%.

Their spectroscopic data (^{1}HNMR, ^{13}C NMR and IR) were in full agreement with those reported in ref.[11]

Compound 4: This compound was synthesized according to the general procedure starting from **12** (32 mg, 0.129 mmol) and (*S*,*S*)-**9**. The reaction was compete after 1 h. Purification by chromatography (SiO_2, hexane/ethyl acetate, 1:1) gave the product (28.8 mg, 65%) (see Table 2, entry 3). $[\alpha]_D^{22} = +118$ ($c = 0.1$, CH_2Cl_2) {ref.[12] $[\alpha]_D = +124$ ($c = 0.15$, CH_2Cl_2)}. Chiral HPLC analysis; OD column (hexane/EtOH, 7:3, 1 mL/min), $t_R = 8.0$ min (93%) and 11.7 min (1.7%). The enantiomeric purity of **4** was estimated to be 96%.

Compound *ent*-4: This compound was synthesized according to the general procedure starting from **12** (33 mg, 0.129 mmol) and (*R*,*R*)-**9**. The reaction was complete after 1 h. Purification by chromatography (SiO_2, hexane/ethyl acetate, 1:1) gave the product (26.6 mg, 60% yield) (see Table 2, entry 4). $[\alpha]_D^{22} = -120$ ($c = 0.1$, CH_2Cl_2) {ref.[12] $[\alpha]_D = -128$ ($c = 0.15$, CH_2Cl_2)}. Chiral HPLC analysis; OD column (7:3 hexane/EtOH, 1 mL/min), $t_R = 11.9$ min (94.5%)

and 7.4 (1.4%) min. The enantiomeric purity of *ent*-**4** was estimated to be 97%.

Their spectroscopic data (^{1}HNMR, ^{13}C NMR and IR) were in full agreement with those reported in ref.[12]

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