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Total syntheses of (S_p)-(+)- and (R_p)-(−)-spiniferin-1, a pair of unusual natural products with planar chirality†

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(S_p)-(+)-Spiniferin-1 and (R_p)-(−)-spiniferin-1, a pair of unusual marine natural products with planar chirality, were firstly synthesized *via* a polyfluoroalkanosulfonyl fluoride induced homoallylic carbocation rearrangement reaction. The chiral resolution and palladium-catalyzed β-H elimination of allylic alcohol derivatives were considered as the key steps of these divergent syntheses.

Bridged-[10]-annulenes have spurred considerable interest in the chemical community not only because of their aromaticity but also because of their planar chirality.[1] Vogel has synthesized many artificial bridged-[10]-annulenes in his pioneering work,[2] but natural products with the bridged-[10]-annulene structural unit are rare. Spiniferin-1 (Fig. 1) has been the first and only known planar-chiral natural product with the skeleton of 1,6-methano[10]annulene up to now.

Spiniferin-1 (**1**) was isolated by Cimino *et al.* in 1975 from the Mediterranean sponge *Pleraplysilla spinifera*, which is present in the Bay of Naples.[3] In 1983, Marshall and Conrow finished the first total synthesis of racemic spiniferin-1 to confirm its planar structure.[4] Recently, a concise and efficient total synthesis of racemic spiniferin-1 was also reported by our group.[5] However, the stereochemistry of naturally occurring spiniferin-1 still remains unclear to date. The interest to determine the absolute stereochemistry of spiniferin-1 and to study the biological activities of each of the enantiomers prompted us to continue the syntheses of the two enantiomers of spiniferin-1. Herein, we report the first total syntheses of (S_p)-(+)- and (R_p)-(−)-spiniferin-1 *via* the polyfluoroalkanosulfonyl fluoride induced homoallylic carbocation rearrangement reaction.

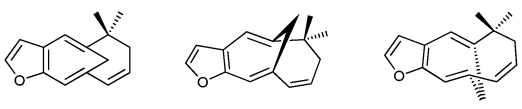

Fig. 1 Structure of spiniferin-1.

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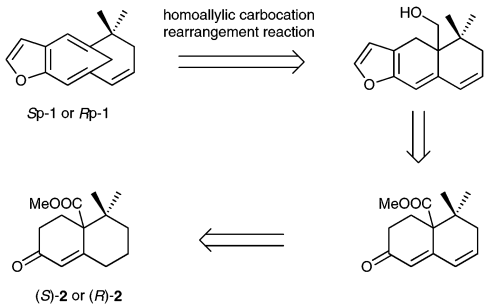


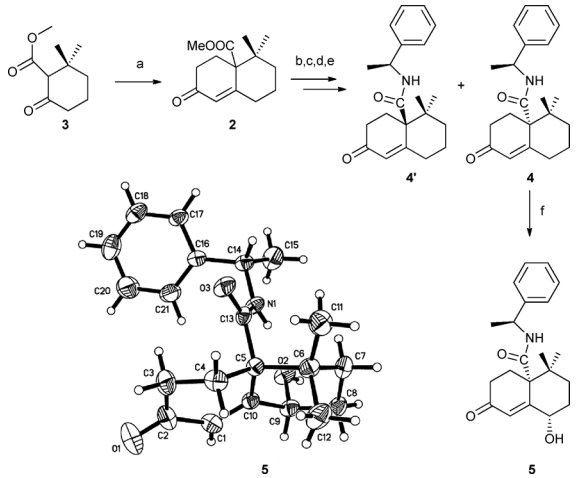
Scheme 1 Retrosynthetic analysis of S_p-(+)- and R_p-(−)-spiniferin-1.

Our retrosynthetic strategy to (S_p)-(+)-**1** and (R_p)-(−)-**1** is shown in Scheme 1. The bridged-[10]-annulene structural units can be easily constructed *via* a polyfluoroalkanosulfonyl fluoride induced homoallylic carbocation rearrangement reaction.[6] The preparation of optically pure synthetic precursor **2** (*S* and *R*) or its derivatives was considered as the main challenge for the successful synthesis.

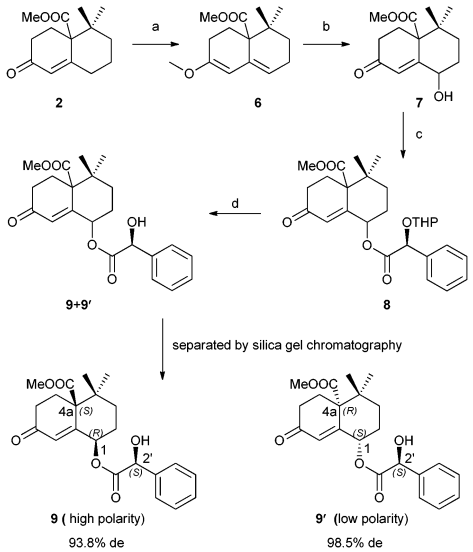
Evidently, enantioselective Michael addition is a direct and concise method for the preparation of optically pure Robinson annulation product **2**.[7] However, the β-keto ester **3** displayed poor reactivity due to the presence of the *gem*-dimethyl group, and its addition to methyl vinyl ketone was only promoted by strong bases such as KOMe or *t*-BuOK (Scheme 2).

Therefore, we turned our attention to the chiral resolution of racemic enone **2**. Much to our disappointment, the resolution of enone **2** *via* formation of an inclusion complex of TADDOL[8] only gave less than 30% ee value under optimized conditions. The chiral ketal of **2** formed by treatment with tartrate ester is also inseparable by recrystallization or chromatography. The diastereomeric amides **4** and **4′** with (*S*)-α-methylbenzylamine as a chiral auxiliary can be readily separated chromatographically, and their absolute stereochemistry was also determined by X-ray analysis of the hydroxylated derivative **5** from amide **4** (Scheme 2). However, all attempts to cleave the amide bond of **4** and **5** to regenerate the C–O single bond, which is necessary for the last step in our strategy, were fruitless because of the presence of the *gem*-dimethyl group, hence precluding the synthesis of enantiomerically pure spiniferin-1 from amide **4**.

Fortunately, we found that the (*S*)-mandelic acid esters **9** and **9′** of γ-hydroxyl enone **7** were easily resolved as well



Scheme 2 Robinson-type annulation of β-keto ester **3** and the resolution of **2** *via* diastereomeric amide formation. *Reagents and conditions*: (a) methyl vinyl ketone, KOMe, 0 °C; K_2CO_3, MeOH, reflux, 80%; (b) $LiAlH_4$, THF, rt, 94%; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C–rt, 91%; (d) $NaClO_2$, $NaH_2PO_4{\cdot}2H_2O$, DMSO, $^tBuOH/H_2O$, 0 °C, 75%; (e) DMF, $(COCl)_2$, (*S*)-α-methylbenzylamine, −20 °C–rt, then resolution by chromatography, **4**: 39%, **4′**: 41%; (f) O_2, orthoformic acid triisopropyl ester, *p*-toluenesulfonic acid, ^{i}PrOH, 40 °C, 87%.



Scheme 3 Synthesis of γ-hydroxyl enone **7** and chiral resolution. *Reagents and conditions*: (a) $CH(OCH_3)_3$, *p*-toluenesulfonic acid, CH_3OH, 0 °C, 78%; (b) oxone, CH_3OH, rt, 80%; (c) *O*-tetrahydropyranyl-*S*-mandelic acid, DCC, DMAP, CH_2Cl_2, 0 °C, 85%; (d) *p*-toluenesulfonic acid, CH_3OH, rt, then resolution by chromatography, **9**: 36%, **9′**: 38%.

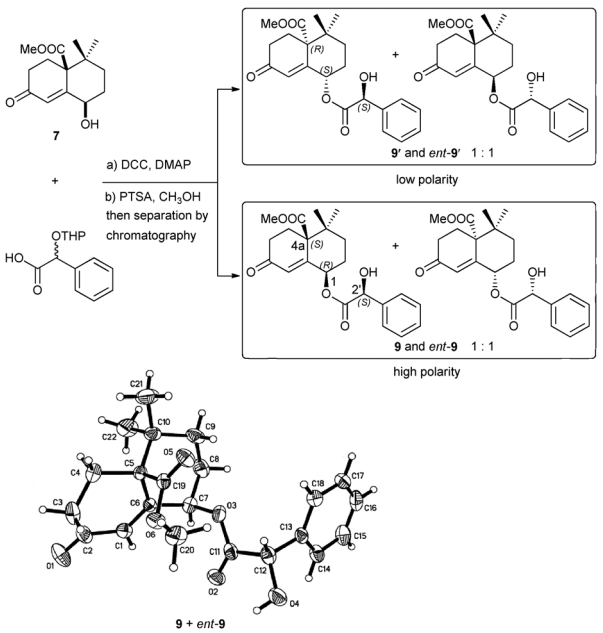


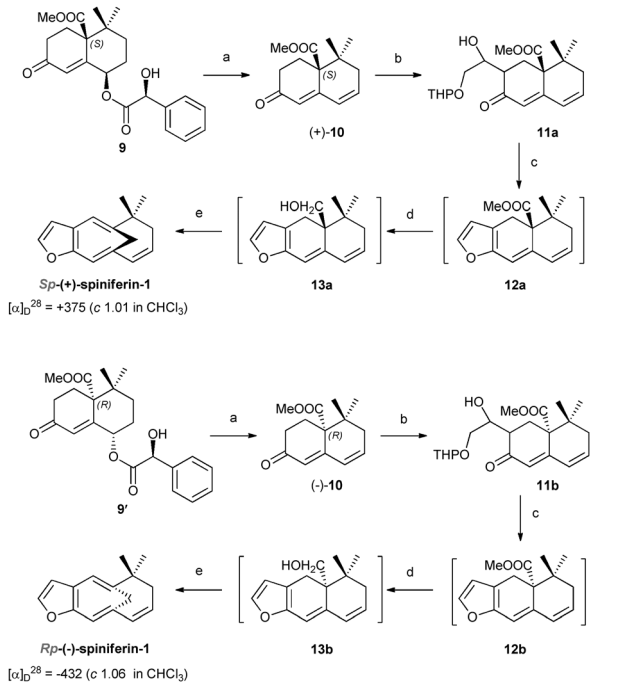
Fig. 2 Synthesis and single-crystal X-ray diffraction analysis of the racemic mixture of **9** and *ent*-**9**.[5]

(Scheme 3). The γ-hydroxyl enone **7** was prepared as a diastereomerically pure *cis*-isomer[5] from enone **2**. Esterification of (±)-**7** with *O*-tetrahydropyranyl-*S*-mandelic acid[9] followed by removal of the THP group afforded more polar ester **9** and less polar ester **9′**, which can be easily separated by flash chromatography.[10]

The absolute configuration of intermediate **9** was assigned in an indirect manner (Fig. 2).[11] The optically pure **9** and **9′** are difficult to recrystallize because of their low melting points. However, the racemic mixture of **9** and its enantiomer (*ent*-**9**), which was prepared from racemic mandelic acid and **7**, had a higher melting point and could be easily recrystallized. X-Ray analysis[5] of the mixture of **9** and *ent*-**9** confirmed the relative stereochemistry of three stereocenters in **9**. Thus, the absolute configurations of **9** and **9′**, derived from (*S*)-mandelic acid, were unambiguously assigned to be 1*R*,4a*S*,2′*S* and 1*S*,4a*R*,2′*S*, respectively, as shown in Scheme 3.

With optically active intermediates **9** (83.6% ee as determined by HPLC) and **9′** (95.5% ee) in hand, we started to synthesize the two enantiomers of spiniferin-1. Selective hydrolysis of mandelic acid ester to regenerate enantiopure **7** in the presence of potassium carbonate or triethylamine[12] was unsuccessful because of the intramolecular transesterification to form a lactone. However, **9** and **9′** can be directly converted into (*S*)-**10** and (*R*)-**10** in high yields *via* $Pd(PPh_3)_4$-catalyzed β-H elimination of the allylic alcohol ester (Scheme 4).[13] Starting from dienone (*S*)-**10** or (*R*)-**10** the two enantiomers of spiniferin-1 were prepared smoothly following the previous procedures for the synthesis of (±)-spiniferin-1. The ^{1}H and ^{13}C NMR data of (+)-spiniferin-1 and (−)-spiniferin-1 were both in agreement with the reported values of racemic spiniferin-1.[3–5] Based on the mechanisms of polyfluoroalkanosulfonyl fluoride induced tandem carbocation rearrangement reaction, the absolute configuration of (+)-spiniferin-1 was assigned as S_p and (−)-spiniferin-1 as R_p.

With the two enantiomers of spiniferin-1 in hand, the stability of the planar chirality was studied. Consistent with Vogel's reports,[14] the planar chirality proves to be stable under neutral conditions. No racemization was observed when the chiral samples were placed at 0 °C for several months or at elevated temperature (60 °C) for one hour. The specific rotation of (−)-spiniferin-1 had no change with time at room temperature (Table 1). Compared with the reported data of



Scheme 4 Syntheses of (+)-spiniferin-1 and (−)-spiniferin-1. *Reagents and conditions*: (a) $Pd(PPh_3)_4$, Et_3N, dioxane, 75 °C, 84% for (+)-**10**, 79% for (−)-**10**; (b) LDA, $ZnCl_2$, $THPOCH_2CHO$, THF, −78 °C, 96% for **11a**, 95% for **11b**; (c) *p*-toluenesulfonic acid, THF, 80 °C; (d) $LiAlH_4$, THF, 40 °C; (e) $CF_3CF_2CF_2CF_2SO_2F$, DBU, THF, 0 °C–rt, 35% 3 steps for (+)-spiniferin-1, 31% 3 steps for (−)-spiniferin-1.

Table 1 Specific rotation of (−)-spiniferin-1[a]

	0 h	6.5 h	15.5 h	33 h
(−)-**1**[b]	−364.2	−365.7	−372.2	−375.2

[a] (−)-Spiniferin-1: *c* = 0.905, MeOH, 25 °C. [b] The slight increase of the specific rotation was due to the slow evaporation of the solvent.

the natural product (−4.2, concentration and solvent not given),[3a] synthetic samples exhibited much higher rotations (+375, *c* 1.01 in $CHCl_3$, 80.6% ee and −432, *c* 1.06 in $CHCl_3$, 90.8% ee).[15] Given the stability of the planar chirality, we surmised that the natural product existed in a nearly racemic form (*ca.* 1% ee).

In conclusion, the first total syntheses of S_p-(+)-spiniferin-1 and R_p-(−)-spiniferin-1 were accomplished and the natural spiniferin-1 was shown to be nearly racemic. The stereochemical study of enantiomerically enriched spiniferin-1 indicated that the naturally occurring planar chirality is stable under mild conditions. The divergent syntheses of (+)-spiniferin-1 and its enantiomer in 5.4% and 4.7% respective overall yields over 9 steps could provide an approach for the large scale preparation of these rare substances for further biological studies. The biological activities of (±)-spiniferin-1, (+)-spiniferin-1, (−)-spiniferin-1 and their analogues are currently under investigation.

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15 The low diastereomeric optical purity of ester **9** or **9′** accounts for the low ee value of (+)-spiniferin-1 or (−)-spiniferin-1 since no further racemization was observed in all the reactions shown in Scheme 4. See ESI† for details.