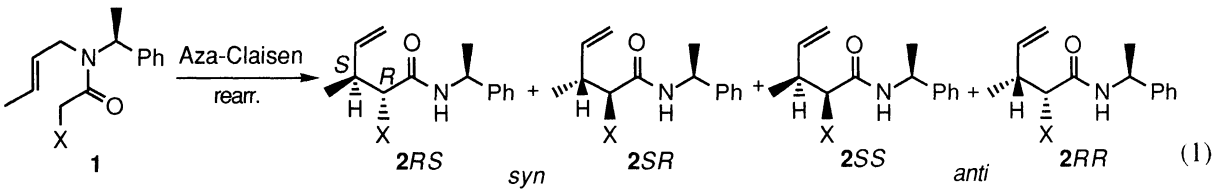
CHEMISTRY LETTERS, pp. 543-546, 1994.

A Stereoselective Synthesis of (-)-Isoiridomyrmecin. Application of the Asymmetric Aza-Claisen Rearrangement

Tetsuto TSUNODA,* Shinji TATSUKI, Kazuko KATAOKA, and Shô ITÔ
Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashirocho, Tokushima 770

(-)-Isoiridomyrmecin was synthesized stereoselectively in 6 steps starting from 1-hydroxymethyl-5-methylcyclopentene and utilizing the asymmetric aza-Claisen rearrangement as a key step.

The recently developed Aza-Claisen rearrangement of the enolate of the carboxamides **1** has the potential for broad use in the stereocontrolled construction of carbon skeletons occurring in nature because of 1) its excellent stereoselectivities (*syn* : *anti* ≥ 99 : 1, *RS* : *SR* ≥ 90 : 10)[1] (eq. 1) and 2) its adaptability to various substituents (X = alkyl, OH, or NH_2 in eq. 1).[2] The potential was demonstrated by short-step syntheses of (-)-verrucarinolactone and *D-allo*-isoleucine.[2]

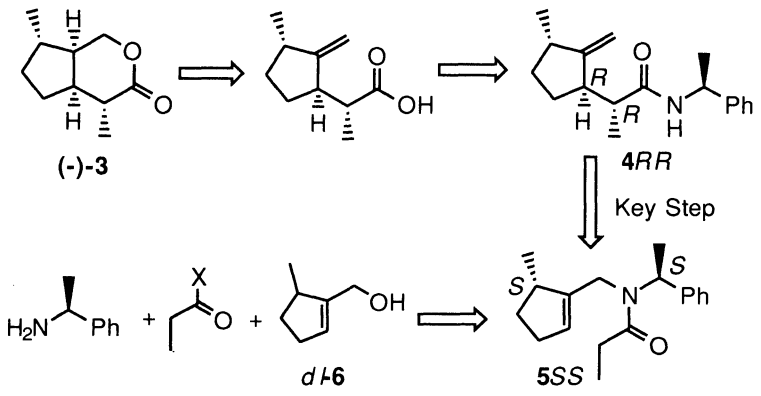


(1)

In a continuing effort to promote this potentially useful reaction, we attempted a highly stereoselective short-step synthesis of (-)-isoiridomyrmecin ((-)-**3**),[3] a constitute of *Actinidia polygama* with a unique activity toward felids. The compound has been an attractive target of many synthetic efforts[4] because of the presence of the 4 contiguous chiral centers in a monoterpenoid carbon skeleton. The results are described herein.

Our synthetic strategy is shown in Scheme 1. The target molecule (-)-**3** can be retrosynthetically converted to the carboxamide **4***RR*, which has exactly the same configuration as in the major product **2***RS* (X = CH_3) in eq. 1, and therefore can be synthesized by the aza-Claisen rearrangement of the carboxamide **5***SS*. In the rearrangement, there would be a favorable double stereodifferentiation due to the (*S*)-1-phenylethyl group and the (*S*)-methyl group on the cyclopentene ring. Thus, the transition state from **5***SS* to **4***RR* (Fig. 1) would be by far more favorable than any other transition states of the different conformations. The precursor **5***SS* can be constructed from the alcohol **6**, a propionic acid derivative, and (*S*)-1-phenylethylamine, which can be utilized in the optical resolution as well as in the asymmetric induction. Thus the synthesis can simply start with *dl*-**6**.

Following the synthetic strategy, *dl*-**6**[5] derived in 3 steps from 2-methylcyclopentanone was condensed with *N*-(*S*)-1-phenylethyltosylamide in the presence of *N, N, N', N'*-tetramethylazodicarboxamide (TMAD)-



Scheme 1.

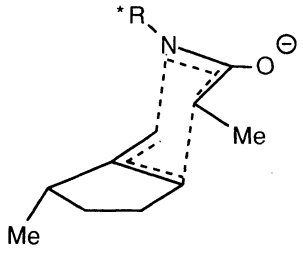
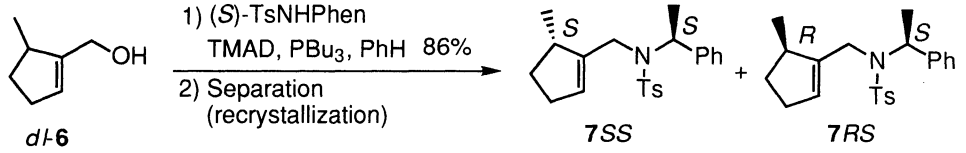


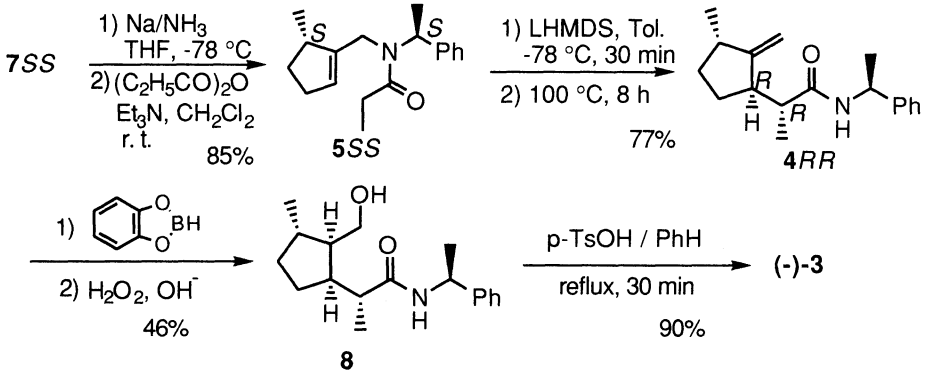
Fig. 1. The most stable transition state in the key step 5*SS* to 4*RR*.

Bu_3P, a Mitsunobu reagent system we developed recently.[6] The product, a crystalline 1 : 1 mixture of the tosylamides 7*SS* and 7*RS* obtained in 86% yield was resolved by recrystallization (hexane),[7] and the structure of 7*SS* was established by X-ray analysis (eq. 2).[8]



(2)

The desired 7*SS* was converted to 5*SS*, the precursor of the aza-Claisen rearrangement, by Birch reduction followed by acylation. The rearrangement of 5*SS* was carried out under the standard conditions[1] to give a single isomer 4*RR* (eq. 3), whose stereochemistry was again determined by X-ray analysis.[9] No trace of the other isomers was detected.[10] The excellent face selectivity observed must be the result of the cooperative double stereodifferentiation of the (*S*)-phenylethyl group and the methyl group on the cyclopentene ring. The effect of the methyl group was found to be ca. 81 : 1 in favor of 4*RR* over 4*SS* from the rearrangement of 5*RS*, the mismatched isomer.[11]



(3)

The NOE experiments on 4*RR* confirmed that the compound existed in the same conformation shown in Fig. 2 in solution as in crystals, and suggested that reagents would attack the double bond from the face opposite to the amide side chain in the molecule (α-side). In fact, hydroboration of 4*RR* occurred exclusively from the α-side to give the alcohol **8**. However, the yield remained rather low with any borane reagents

because of the concurrent reduction of the amide part to an amino group.

Acid hydrolysis of **8** afforded in good yield (-)-**3**, mp 54-56 °C, $[\alpha]_D^{23}$ - 62.7 (c 0.22, CCl_4), whose physical properties compared well with those in the literature [mp 58-59 °C, $[\alpha]_D^{17}$ -62 (c 1.01, CCl_4)][3b, c] (eq. 3).

Thus, the usefulness of aza-Claisen rearrangement was amply demonstrated by the efficient synthesis of (-)-isoiridomyrmecin.

Acknowledgment: The authors wish to thank Michiyo Sambu, Yurika Shimasaki, and Takayuki Yamada of our Faculty for their enthusiastic collaboration at various stages of the present study.

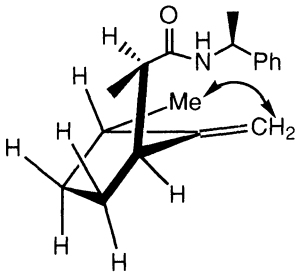


Fig. 2. Conformation of **4*RR*** determined by NOE (arrow).

References

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2) T. Tsunoda, S. Tatsuki, Y. Shiraishi, M. Akasaka, and S. Itô, *Tetrahedron Lett.*, **34**, 3297 (1993).

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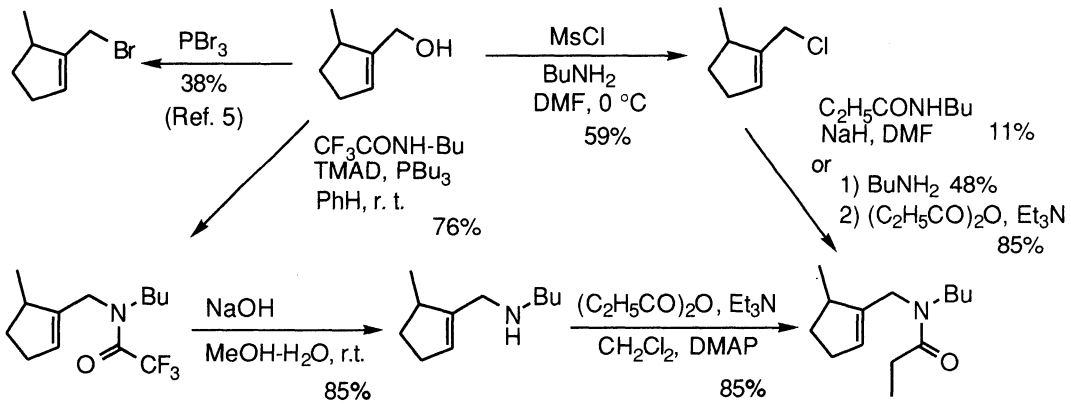
5) A. J. Barker and G. Pattenden, *J. Chem. Soc., Perkin Trans I*, **1983**, 1901.

6) T. Tsunoda, J. Otsuka, Y. Yamamiya, and S. Itô, Preceding paper. Also see T. Tsunoda, Y. Yamamiya, and S. Itô, *Tetrahedron Lett.*, **34**, 1639 (1993). Usefulness of the new reagent system in the synthesis of secondary allylic amine is also clear from the reaction sequence shown here.



When the new Mitsunobu reagents were applied to *N*-(*S*)-1-phenylethyltrifluoroacetamide under the standard conditions, however, the *O*-alkylation product was obtained predominantly, probably due to the steric hindrance around the amide nitrogen.

7) All new compounds were characterized by NMR, IR, Mass, $[\alpha]_D$ and elemental analyses.

8) The compound **7*SS***, $C_{22}H_{27}NO_2S$, MW = 369.53, crystallizes in orthorhombic system of the space group $P2_12_12_1$ with 4 molecules in a unit cell of the dimensions, a = 9.917(3), b = 21.519(5), c = 9.845(2) Å. Data were collected on a MacSience MXC18 diffractometer using CuKα radiation. Reflections measured: 1410; reflections used: 1275. The final R and R_w factors were 4.8% and 5.2%, respectively. The molecule structure deduced is shown in Fig. 3.

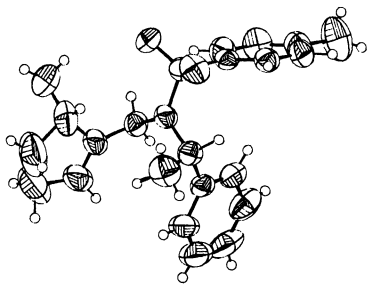


Fig. 3. Molecular structure of **7*SS***.

9) X-ray data for **4*RR***, $C_{18}H_{25}NO$, MW = 271.41, monoclinic system, space group C_2, a = 21.295(4), b = 4.991(1), c = 16.879(3) Å, β = 107.99(1)°, Z = 4. Data were collected as in Ref. 8. Reflections measured: 1422; reflections used: 1260. The final R factor: 5.8%, the final R_w: 7.2%. The molecular structure deduced is shown in Fig. 4.

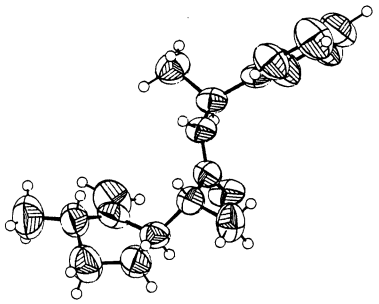
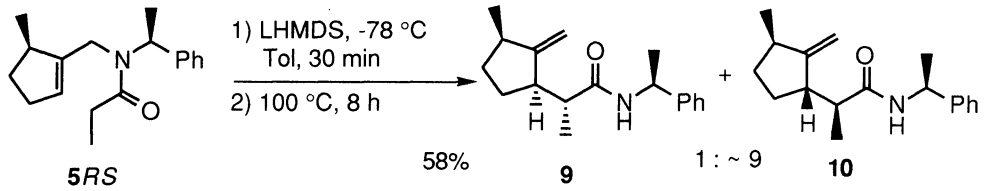


Fig. 4. Molecular structure of **4*RR***.

10) The purity and the ratio of stereoisomers in the products were determined by capillary GLC.

11) The facial selectivity due to the methyl group on the cyclopentene ring was estimated as follows. The rearrangement of the mismatched isomer **5** *RS* derived from **7*RS*** afforded a 1 : 9 mixture of **9** and **10** in 58% yield. The stereochemistry of **10** was confirmed by an X-ray crystallographic analysis.



Since the directing effect of the methyl group overcomes that of the phenylethyl group (9 : 1) by the factor of 9, the net effect of the former is 81. Using this factor, the product ratio (**4*RR*** : **4*SS***) in the reaction of the matched isomer **5*SS*** was estimated to be 729 : 1, supporting the observation that no other isomer was detected in the reaction mixture.

(Received December 22, 1993)