Pure & Appl. Chem., Vol. 66, Nos 10/11, pp. 2071–2074, 1994.
Printed in Great Britain.

Application of the aza-Claisen rearrangement to the total synthesis of natural products: (–)-Isoiridomyrmecin

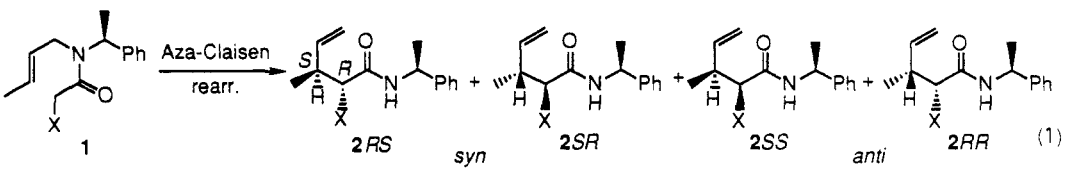
Shô Itô and Tetsuto Tsunoda

Faculty of Pharmaceutical Sciences, Tokushima Bunri University,
Yamashirocho, Tokushima, 770 Japan.

Abstract: Utilizing the aza-Claisen rearrangement recently developed by the authors, a straightforward synthesis of (-)-isoiridomyrmecin was achieved. A new reagent system, TMAD-Bu_3P in benzene, was developed en route for the Mitsunobu type of the reactions. This system was found to be more effective to the nucleophiles of wider pK_a range. The stable phosphoranes were also found to be effective in this type of reactions.

INTRODUCTION

Although many stereoselective reactions have been developed in the last three decades, discovery of more effective reactions is still one of the most important contributions in synthetic organic chemistry today. The aza-Claisen rearrangement of the carboxamide enolates **1** to the amides **2** recently developed by us has potential for broad use in the stereocontrolled construction of the carbon skeletons occurring in nature because of its excellent stereoselectivities (*syn* : *anti* ≥ 98 : 2, *RS* : *SR* ≡ 90 : 10) (1) and versatility (X = alkyl, OH, or NH_2) (eq. 1) (2).



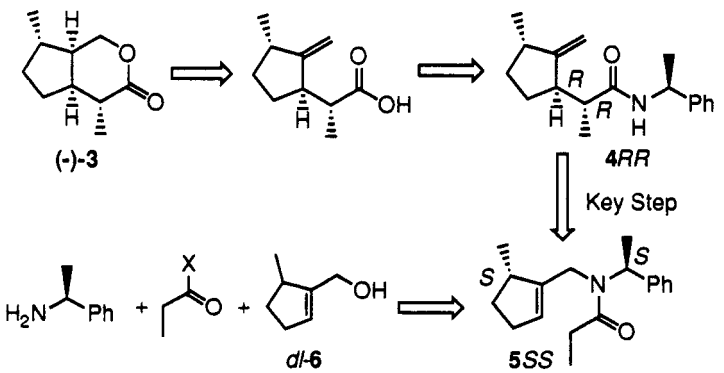
(1)

In order to demonstrate its applicability to the synthesis of natural products, we synthesized (-)-isoiridomyrmecin ((-)-**3**) (3), a constituent of *Actinidia polygama* exhibiting unique bioactivity toward felids. The compound has been a target of many synthetic efforts (4) because of the presence of 4 contiguous chiral centers in a monoterpenoid carbon skeleton.

SYNTHETIC STRATEGY

Our synthetic strategy is shown in Scheme. 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-phenethyl group and the (*S*)-methyl group on the cyclopentene ring. Thus the transition state from **5***SS* to **4***RR* (Fig. 1) would be much more stable than any other ones of the different conformations. The precursor **5***SS* can be constructed from the alcohol **6**, a propionic acid derivative, and (*S*)-1-phenethylamine. The amine can be utilized in the optical resolution as well as in the asymmetric induction. Thus the synthesis can simply start with *dl*-**6**.

Scheme.



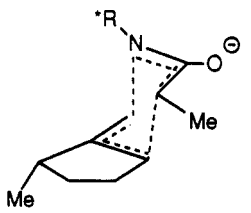
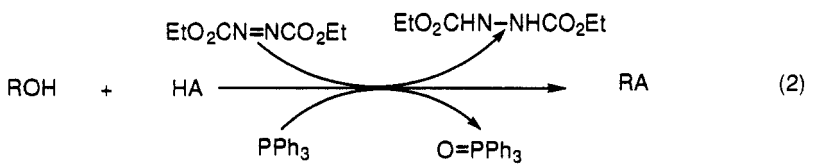
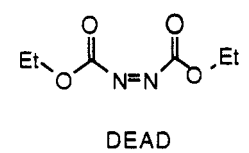


Fig. 1. The most stable transition state in the key step **5***SS* to **4***RR*

DEVELOPMENT OF TMAD, A NEW MITSUNOBU REAGENT

The biggest problem in performing an aza-Claisen rearrangement is the preparation of the pure precursors, *N*-allylic *N*-alkylacylamides. Although many pure allylic alcohols are easily available, the amides obtained from them through halides or tosylates are generally impure and need tedious purification. The Mitsunobu reaction (eq. 2) is an alkylation reaction which does not require any prerequisite activation of alcohols (5). However, the traditional Mitsunobu reagent, DEAD, does not alkylate amines or carboxamides because of the weak acidity of their hydrogens, and the corresponding sulfonamides have to be used. Even then the overall yield is generally not excellent (6). Therefore, we developed a new reagent system, TMAD-Bu_3P in benzene in place of DEAD-PPh_3 in THF, after detailed analysis of the generally accepted mechanism of the reaction (7). A few examples of its application are shown in the Table 1 along with those of DEAD-PPh_3.




DEAD

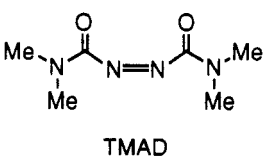

TMAD

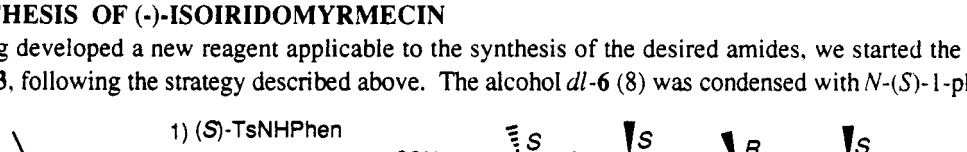
Table 1. Mitsunobu Alkylation (% Yield of RA).

HA	TsNHMe		$F_3CONHBn$		$H_2C(CO_2Et)_2$	
ROH	D	TM[1]	D	TM	D	TM
C_4H_9OH	65	100	–	83	–[2]	45
$C_6H_{13}CHCH_3$ OH	53	40	–	11	–	*[3]
$MeCH=CHCH_2OH$	51	96	–	78	–	–

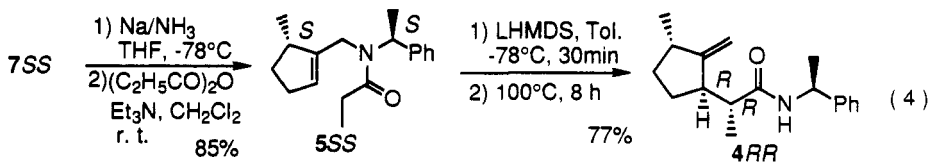
1. D: DEAD-TPP in THF, r.t., 24h, TM: TMAD-TBP in PhH, r.t., 24h. 2. – : no experimental result. 3. *: very low or no yield of the desired product.

SYNTHESIS OF (-)-ISOIRIDOMYRMECIN

Having developed a new reagent applicable to the synthesis of the desired amides, we started the synthesis of (-)-**3**, following the strategy described above. The alcohol *dl*-**6** (8) was condensed with *N*-(*S*)-1-phenethyl-



tosylamide in the presence of TMAD-Bu_3P. A crystalline 1 : 1 mixture of the tosylamides 7*SS* and 7*RS* thus obtained was separated by recrystallization (hexane) (eq. 3). The desired 7*SS*, with its structure established by an X-ray crystallographic analysis, was converted to 5*SS*, the precursor of the aza-Claisen rearrangement, by Birch reduction followed by acylation (eq. 4).



The rearrangement of 5*SS* conducted under standard conditions (1) yielded a single isomer 4*RR*, whose stereochemistry was again determined by an X-ray analysis (eq. 4). No trace of the other stereoisomers was detected. The excellent facial selectivity must be the result of the synergistic double stereodifferentiation of the (*S*)-1-phenethyl group and the methyl group on the cyclopentene as anticipated before.

NOE experiments on 4*RR* revealed that the compound existed in the conformation shown in Fig. 2 in solution, suggesting that reactions on the double bond would occur from the side opposite to the amide chain in the molecule (α-side). In fact, hydroboration occurred exclusively from the α-side to give the alcohol **8**. However, the yield was rather low because of the concomitant reduction of the amide group to an amino group. Acid hydrolysis of **8** afforded in good yield a lactone, mp.54-56°C, $[\alpha]_D^{23}$-63 (c 0.22, CCl_4), whose physical properties compared well with those of natural (-)-**3** [mp 58-59°C, $[\alpha]_D^{23}$ -62 (c 1.01, CCl_4)] (3b, 3c) (eq. 5).

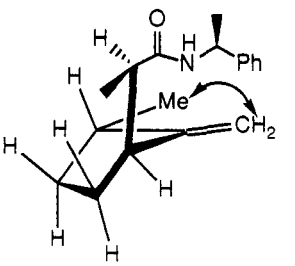
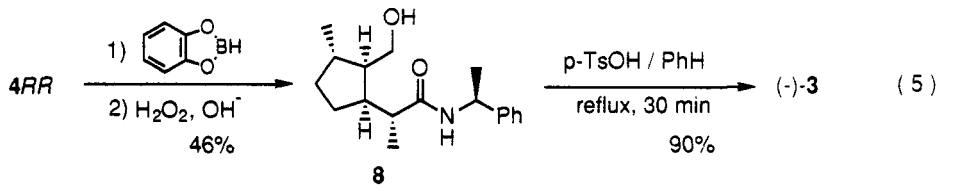


Fig. 2. Conformation of 4*RR* determined by NOE (arrow)



NEW ALKYLATION REACTIONS WITH PHOSPHORANES

The structural similarity between one of the proposed intermediates (eg. **9**) in the Mitsunobu reaction and the stable phosphonium ylides (eg. **10**), and the probable similarity in their behavior towards alcohols and nucleophiles (eq. 6 and 7) prompted us to investgate the direct *N*-, *O*- and *C*-alkylation by alcohols using the phosphorane **11** (1.5 equivalents) instead of the azodicarboxylic acid derivatives (eq.7). The results are listed in Table 2.

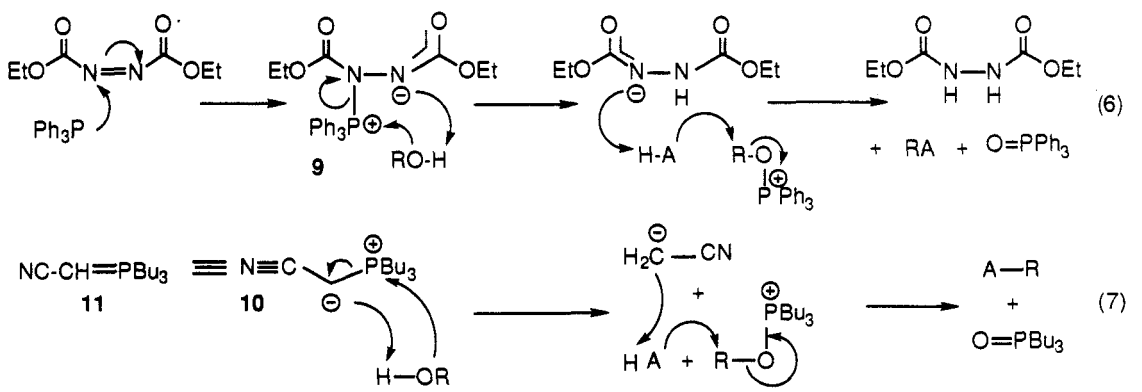


Table 2. *N*-, *O*- and *C*-Alkylation with phosphorane **11**

H-A	TsNHMe (pK_a 11.7)			$F_3CCONHCH_2Ph$ (pK_a 13.6)			PhCOOH (pK_a 4.2)		$NCCH_2SO_2Ph$		
Reagent[a]	D	T	B	D	T	B	D	B	D	T	B
R-OH Temp. (°C)	r.t.	r.t.	100	r.t.	r.t.	100	r.t.	100	r.t.	r.t.	100
$PhCH_2OH$	66	99	100	3	86	68	—	100	60	59	77
C_4H_9OH	65	100	100	—	83	75	85[b]	99	—	63	96
$C_6H_{13}CHCH_3$ OH	53	40	89	—	11	4	20[b]	96	20	23	66
$H_3CCH{=}CHCH_2OH$	51	96	100	—	78	79	85[b]	90	—	64	89

a. D: DEAD-PPh_3 / THF, T: TMAD-Bu_3P / PhH, B: **11** / PhH. b. Ref. 5

Although the reaction is slower and needs higher temperature for the completion than the Mitsunobu type reagents, **11** tends to promote the alkylation with primary alcohols in comparable yields as TMAD. The characteristic feature of **11**, however, is its capability of alkylation with secondary alcohol. The fact implies phosphoranes to be a potentially useful new alkylating reagent. Studies on the nature of the reaction including its stereochemical outcome are in progress.

ACKNOWLEDGEMENT

The authors wish to thank Keiko Arita, Kazuko Kataoka, Miwa Nagaku, Junko Otsuka, Fumie Ozaki, Michiyo Sambu, Yurika Shimasaki, Shinji Tatsuki, Takayuki Yamada, Hidetoshi Yamamoto, and Yoshiko Yamamiya of our Faculty for their enthusiastic collaboration at various stages of the present study.

REFERENCES

1. T. Tsunoda, O. Sasaki and S. Itô. *Tetrahedron Lett.* **31**, 727 (1990). S. Itô and T. Tsunoda. *Pure & Appl. Chem.* **62**, 1405 (1990). *Idem. J. Chinese Chem. Soc.* **39**, 205 (1992). T. Tsunoda, M. Sakai, O. Sasaki, Y. Sako, Y. Hondo and S. Itô. *Tetrahedron Lett.* **33**, 1651 (1992).
2. T. Tsunoda, S. Tatsuki, Y. Shiraishi, M. Akasaka and S. Itô. *Tetrahedron Lett.* **34**, 3297 (1993).
3. a. T. Sakan, F. Murai, S. Isoe, S. B. Hyeon and Y. Hayashi. *Nippon Kagaku Zasshi* **90**, 507 (1969). b. G. W. K. Cavill, D. L. Ford and H. D. Locksley. *Austral. J. Chem.* **9**, 288 (1956). c. G. W. K. Cavill and H. D. Locksley. *ibid.* **10**, 352 (1957).
4. Syntheses of *dl*-**3**: P. Callant, R. Ongena and M. Vandewalle. *Tetrahedron* **37**, 2085 (1981). M. Abelman, R. L. Funk and J. D. Munger, Jr. *J. Am. Chem. Soc.* **104**, 4030 (1982). P. A. Wender and G. B. Dreyer. *Tetrahedron Lett.* **24**, 4543 (1983). T. F. Wang and C. F. Yang. *J. Chem. Soc., Chem. Commun.* 1876 (1989). K. Mikami, K. Takahashi and T. Nakai. *Synlett.* 45 (1989). J. D. Kilburn. *Tetrahedron Lett.* **31**, 2193 (1990). Syntheses of optically active **3**: K. J. Clark, G. I. Fray, R. H. Jaeger and R. Robinson. *Tetrahedron* **6**, 217 (1959). J. Wolinsky, T. Gibson, D. Chan and H. Wolf. *Tetrahedron* **21**, 1247 (1965). J. M. Takacs and Y. C. Myoung. *Tetrahedron Lett.* **33**, 317 (1992). D. Tanaka, T. Yoshino, I. Kouno, M. Miyashita, and H. Irie. *Tetrahedron* **43** 10253 (1993).
5. O. Mitsunobu. *Synthesis* 1 (1981)
6. J. R. Henry, L. R. Marcin, M. C. McIntosh, P. M. Scola, G. D. Harris Jr. and S. M. Weinreb. *Tetrahedron Lett.* **30**, 5709 (1989). M. L. Edwards, D. M. Stenerick and J. R. McCarthy. *ibid.* **31**, 3417 (1990)
7. See T. Tsunoda, Y. Yamamiya and S. Itô. *Tetrahedron Lett.* **34**, 1639 (1993).
8. A. J. Barker and G. Pattenden. *J. Chem. Soc. Perkin Trans I*, 1901 (1983).