1,2-Asymmetric Induction in the Intramolecular [2+2] Cycloadditions of Keteniminium Salts. Enantioselective Syntheses of (-)-Dihydroactinidiolide and (-)-Anastrephin

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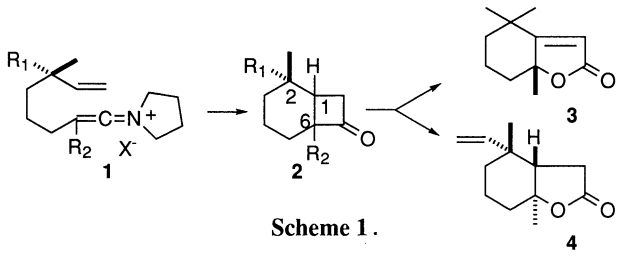
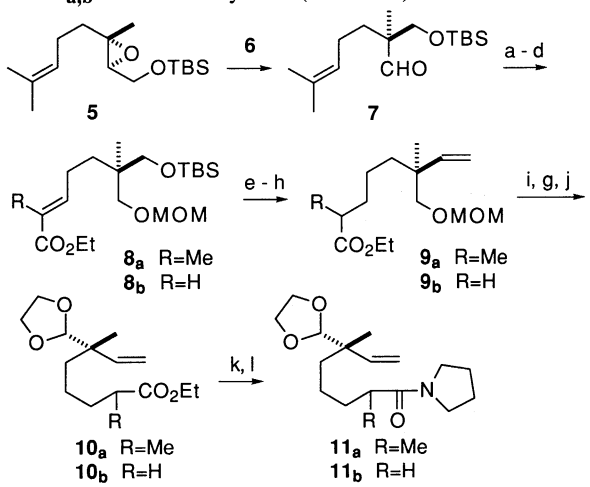
1,2-Asymmetric induction in the intramolecular [2+2] cycloadditions of the keteniminium salts resulted in the preferential formation of optically pure bicyclo[4.2.0]octan-7-ones (**13a,b**). These cycloadducts, **13a** and **13b**, were successfully converted into the key intermediates of (-)-dihydroactinidiolide and (-)-anastrephin, respectively.

Although the synthetic importance of the intramolecular version of [2+2] cycloadditions of kenteniminium salts[1] with alkenes in the synthesis of various carbocyclic[2] and heterocyclic systems[3] has been recognized in recent years, practical examples of the 1,2-asymmetric induction[3b] via the cycloaddition are few. Our interest was, therefore, in 1,2-asymmetric induction of the chiral substrates **1** with a quaternary stereogenic center at the α-carbon (C-2) of alkene part in order to achieve stereochemical control at the ring juncture (C-1 and C-6) of the cycloadducts, bicyclo[4.2.0]octan-7-ones **2**, which would be generally useful intermediates for the synthesis of enantiomerically pure natural products. We now report the intramolecular [2+2] cycloaddition-based 1,2-asymmetric induction and an application of the strategy in the enantioselective syntheses of naturally occurring insects pheromones, (-)-dihydroactinidiolide **3**[4] and (-)-anastrephin **4**.[5] (Scheme 1)



Scheme 1.

According to the protocol of Yamamoto,[6] reaction of the epoxy silyl ether **5**, prepared by the Sharpless asymmetric epoxidation of geraniol using L-(+)-diethyl tartrate followed by silylation, with methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) **6** provided the aldehyde **7** with (*S*)-configuration in 97% yield (95% ee). The quaternary stereogenic center present in **1** was thus constructed. On sequential sodium borohydride reduction, MOM protection, ozonolysis, and Wittig reaction, **7** was converted into the two types of unsaturated esters $\mathbf{8_{a,b}}$ in good overall yields. Reduction of the double bond in $\mathbf{8_{a,b}}$, desilylation, Swern oxidation, followed by Wittig olefination provided $\mathbf{9_{a,b}}$. Subsequent deprotection of the MOM ether followed by Swern oxidation gave the corresponding aldehydes, which were immediately exposed to the conditions of Noyori acetalization reaction[7] to afford $\mathbf{10_{a,b}}$ in 98% and 85% yield, respectively. After saponification of the ester in $\mathbf{10_{a,b}}$ with lithium hydroxide, the resulting carboxylic acid was treated with pyrrolidine, Py-BOP®, HOBT, and triethylamine[8] to provide the amides $\mathbf{11_{a,b}}$[9] in excellent yields. (Scheme 2)

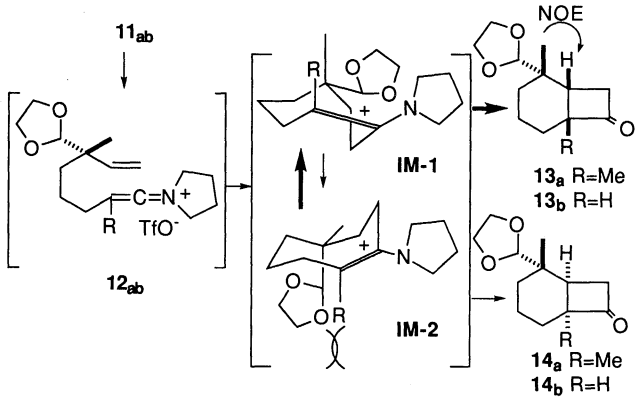


(a) $NaBH_4$, EtOH, 0°C, 95%; (b) MOMCl, $^iPr_2NEt$, r.t., 97%; (c) O_3, CH_2Cl_2 then Me_2S, -78°C; (d) $Ph_3P{=}C(Me)CO_2Et$, benzene reflux, 92% for $\mathbf{8_a}$, 91% for $\mathbf{8_b}$; (e) H_2, 10% Pd-C, EtOH, r.t.; (f) $^nBu_4NF$, THF, r.t.; (g) Swern ox., CH_2Cl_2, -78°C; (h) $Ph_3P{=}CH_2$, THF, 0°C, 82% for $\mathbf{9_a}$, 85% for $\mathbf{9_b}$; (i) c.HCl, EtOH, reflux; (j) $TMSO(CH_2)_2OTMS$, TMSOTf, CH_2Cl_2, -78°C, 98% for $\mathbf{10_a}$, 85% for $\mathbf{10_b}$; (k) LiOH, THF, H_2O, reflux; (l) pyrrolidine, Py-BOP®, HOBT, Et_3N, DMF, r.t., 100% for $\mathbf{11_a}$, 96% for $\mathbf{11_b}$.

Scheme 2.

The key cycloaddition was carried out by treatment of $\mathbf{11_{a,b}}$ with triflic anhydride in the presence of collidine in refluxing benzene[10] to give, after hydrolytic workup, the chromatographically separable mixture of the cyclobutanones **13** and their diastereoisomers **14** in a ratio of 5:1 ($\mathbf{13_a}$:$\mathbf{14_a}$)[11] and 3:1 ($\mathbf{13_b}$:$\mathbf{14_b}$), respectively. As anticipated from the precedents,[2a] the chemical yield for the reaciton of $\mathbf{11_b}$ was lower than that of $\mathbf{11_a}$. The configuration of the newly created stereogenic center (C-1) was firmly established by NOE between the C-2 methyl and the methine proton at C-1 in the major diastereoisomers **13**. The diastereoselectivity in the cycloaddition may be rationalized by considering the stepwise keteniminium cyclization process[12] through the eight-membered cationic enamine intermediates (IM-1 and -2).[3b,13] That is to say, IM-1, leading to $\mathbf{13_{a,b}}$, would be more sterically favored than IM-2, that provides $\mathbf{14_{a,b}}$. The

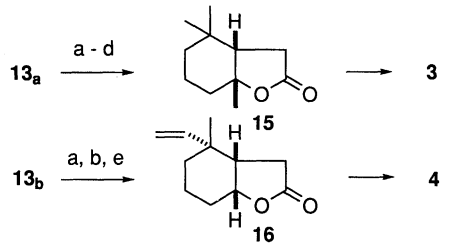
lowered selectivity for $\mathbf{11_b}$ could also be explained by this model as shown in Scheme 3.



R	Yield/%	Ratio of 13/14
Me	75	5/1
H	30	3/1

Scheme 3.

Having established that the 1,2-asymmetric induction during the cycloaddition occurred with moderate selectivity, we next addressed the transformation of the cycloadducts into natural products. Baeyer-Villiger oxidation of $\mathbf{13_a}$ gave the lactone, which, after hydrolysis, was led to the formation of **15**, whose spectral properties and the optical rotation {$[\alpha]_D^{24}$ -60.0°, lit.[4c] $[\alpha]_D^{24}$ -66.1°} are identical with those reported, by a standard manipulations. Since the bicyclic lactone **15** had already been converted into (-)-dihydroactinidiolide **3** by Mori,[4c] the total synthesis of it was formally completed. On the other hand, the conversion of $\mathbf{13_b}$ into the lactone **16**, a key intermediate for the total synthesis of (-)-anastrephin **4** by Tadano,[5] was accomplished by sequential Baeyer-Villiger oxidation, acidic hydrolysis, and Wittig methylenation. ^{1}H NMR, IR, and Mass spectral data of our synthetic **16**,{$[\alpha]_D^{24}$ -71.0°, lit.[5b] $[\alpha]_D^{29}$ -73.3°}, were identical with those of authentic material. (Scheme 4)



(a) *m*-CPBA, $KHCO_3$, CH_2Cl_2, r.t., 74% for **15**, 76% for **16**; (b) aq. AcOH, 90 °C, 80% for **15**, 84% for **16**; (c) $TsNHNH_2$, THF, reflux; (d) $Na(CN)BH_3$, *p*-TsOH, DMF, sulforane, 140°C, 33% for 2 steps; (e) $Ph_3P{=}CH_2$, THF, r.t. 80%.

Scheme 4

Thus, we explored the capabilities of 1,2-asymmetric induction in the intramolecular [2+2] cycloaddition of keteniminium salt and demonstrated the validity of the methodology for assembling the natural pheromones.

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11 **13_a**: Colorless oil, $[\alpha]_D^{24}$ +51.72° (*c* 0.82, $CHCl_3$); IR ($CHCl_3$) 1768 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.97 (3H, s), 1.14 (3H, s), 1.46-1.66 (6H, m), 1.89 (1H, dd, J=10.5 and 8.5 Hz), 2.63 (1H, dd, J=16.4 and 8.5 Hz), 3.25 (1H, dd, J=16.4 and 10.5 Hz), 3.73-3.94 (4H, m), 4.44 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.85, 20.55, 20.91, 28.18, 29.33, 35.94, 38.18, 44.85, 59.70, 65.09, 65.64, 109.58, 212.30; MS *m/z* 224 (M^+); HR MS Found: 224.1400. Calcd for $C_{13}H_{20}O_3$: 224.1411. **14_a**: Colorless oil, $[\alpha]_D^{24}$ +97.65° (*c* 1.70, $CHCl_3$); IR ($CHCl_3$) 1768 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (3H, s), 1.17 (3H, s), 1.39-1.89 (6H, m), 2.20 (1H, dd, J=10.4 and 9.0 Hz), 2.75 (1H, dd, J=16.4 and 9.0 Hz), 3.10 (1H, dd, J=16.4 and 10.4 Hz), 3.83-4.01 (4H, m), 4.72 (1H, s); MS *m/z* 224 (M^+); HR MS Found: 224.1410. Calcd for $C_{13}H_{20}O_3$: 224.1411.

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