A NOVEL SYNTHESIS OF BENZO- AND INDOLO[A]QUINOLIZIDINES BY
INTRAMOLECULAR DIELS-ALDER REACTION OF 1-AZADIENES

Masataka Ihara,[a] Tomoko Kirihara,[a] Akihiro Kawaguchi,[a]
Keiichiro Fukumoto,[a]* and Tetsuji Kametani[b]*

a) Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980,
Japan  b) Institute of Medicinal Chemistry, Hoshi University, Ebara
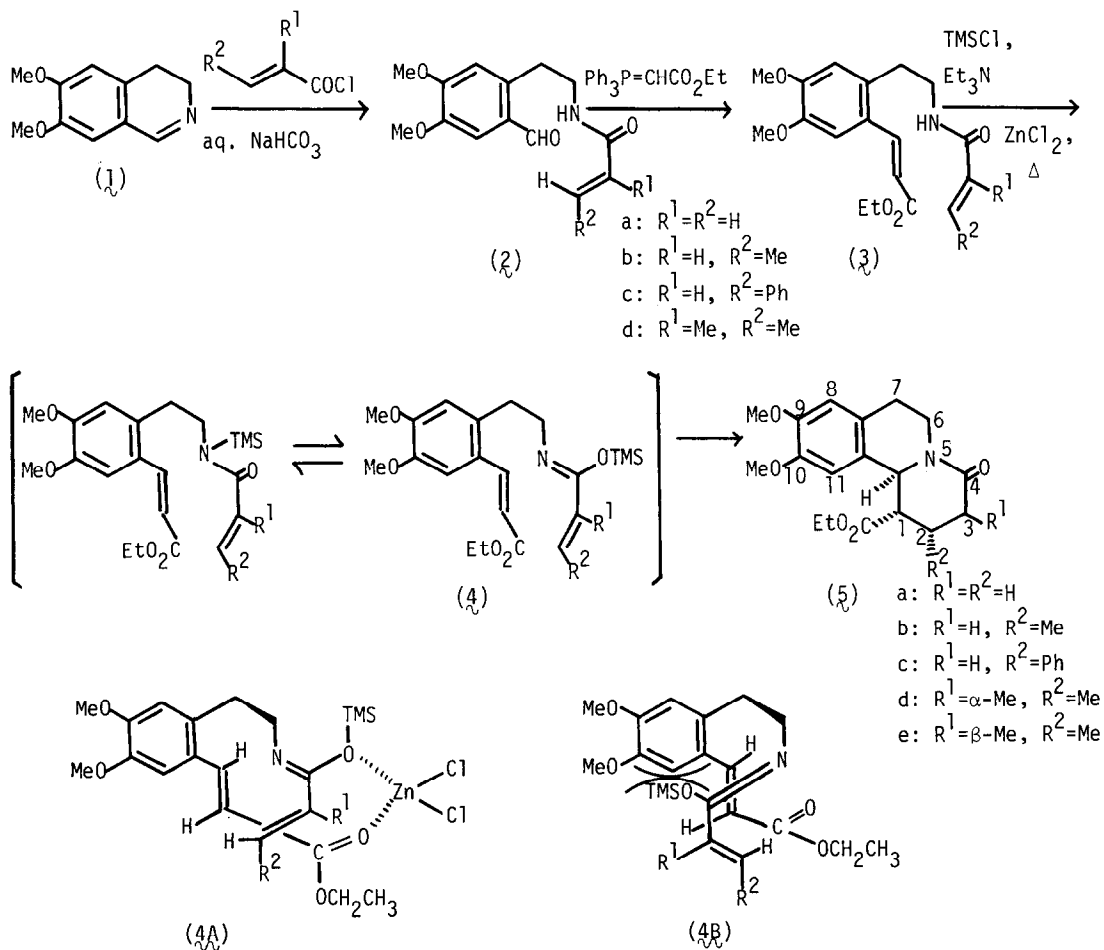2-4-41, Shinagawa-ku, Tokyo 142, Japan

Summary:  Intramolecular Diels-Alder reaction of 1-azadienes was conducted by
heating the $\alpha,\beta$-unsaturated amides ($2a \sim d$ and $6$) in the presence of trimethyl-
chlorosilane, triethylamine and zinc chloride to give benzo- and indolo[a]-
quinolizidines ($5a \sim e$ and $7$).

   Intramolecular Diels-Alder reaction is one of the most powerful methods for
syntheses of polycyclic ring systems with stereocontrol.[1]  It is expected that
the intramolecular cycloaddition of 1-azadienes[2] provides a useful tool for the
construction of quinolizidines and indolizidines, common frameworks of many
alkaloids.  However only few examples[3,4] are so far known mainly due to the
difficult formation of 1-azadienes and its scarce reactivity.  We have investi-
gated the formation of such systems from $\alpha,\beta$-unsaturated amides and the subse-
quent cycloaddition.  Here a novel and facile synthesis of benzo- and indolo-
[a]quinolizidines according to this strategy is disclosed.
   Formation of the formyl $\alpha,\beta$-unsaturated amides ($2a \sim d$)[5] was achieved by the
reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline ($1$) and $\alpha,\beta$-unsaturated acid
chlorides in a mixture of dichloromethane and saturated sodium hydrogencarbo-
nate aqueous solution at room temperature.  Wittig reaction of the aldehydes
($2a \sim d$) with triphenylphosphinecarboethoxymethylene in tetrahydrofuran gave
the unsaturated esters ($3a \sim d$).[5]  The cycloaddition through $4$ was accomplish-
ed by heating the mixture of the unsaturated esters ($3a \sim d$), trimethylchloro-
silane, triethylamine and zinc chloride in toluene at 170 - 180°C in a sealed
tube or refluxing the mixture in o-dichlorobenzene.  A typical experiment was
carried out as follows.  A mixture of $3d$ (150 mg), trimethylchlorosilane (1 ml),
triethylamine (1 ml) and anhydrous zinc chloride (100 mg) in o-dichlorobenzene
(5 ml) was refluxed for 16 hr.  After dilution with benzene, the resulting mix-
ture was washed well with 1% hydrochloric acid.  Usual work up followed by
purification by silica gel column chromatography afforded two products, ($5d$)[5]
(25% yield) and ($5e$)[5] (41% yield).  No formation of the desired quinolizidines

was observed without zinc chloride.[6]

Under similar reaction conditions, the unsaturated esters ($3a \sim c$) were transformed into the tricyclic compounds, ($5a$)[5] (44% yield), ($5b$)[5] (52% yield) and ($5c$)[5] (47% yield) as a single stereoisomer, respectively. Stereochemistry of products were determined on the basis of the following reasons. The coupling constant (J = 8 Hz) of the hydrogen at the $C_{11b}$ position of $5a$ resonated at 5.03 ppm clearly indicates that two hydrogens at the $C_1$ and $C_{11b}$ positions are trans. Treatment of $5e$ with sodium hydride in hot tetrahydrofuran caused epimerization to form $5d$. From the consideration of the transition states, the intermediate ($4B$) leading to the 2β-substituent would be disfavored because of a severe nonbonded interaction between the aromatic ring and the silyl group. On the other hand, the intermediate ($4A$) leading to 2α-substituent would be assisted by chelation with zinc.[7,8] Furthermore the observation of ethyl group of $5c$ and $5e$ at shielded fields suggests a boat conformation of ring C in these two molecules.



a: $R^1=R^2=H$
b: $R^1=H$, $R^2=Me$
c: $R^1=H$, $R^2=Ph$
d: $R^1=Me$, $R^2=Me$

($2$)    ($3$)

($4$)

($5$)    a: $R^1=R^2=H$
b: $R^1=H$, $R^2=Me$
c: $R^1=H$, $R^2=Ph$
d: $R^1=\alpha$-Me, $R^2=Me$
e: $R^1=\beta$-Me, $R^2=Me$

($4A$)    ($4B$)

The unsaturated ester (6)[5] was also prepared from 3,4-dihydro-β-carboline and similarly subjected to the intramolecular cycloaddition to produce the indolo[a]quinolizidine (7)[5] in 58% yield.  Thus an effective synthesis of benzo- and indolo[ā]quinolizidines has been developed.  Application of this method to the synthesis of several natural products are in progress.
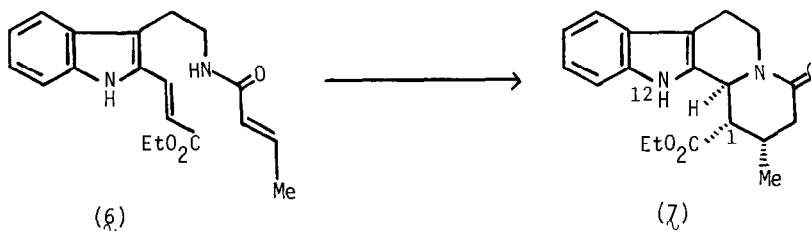


(6)                                    (7)

References and Notes

1)  Review: A. G. Fallis, Can. J. Chem., 62, 183 (1984) and references cited therein.

2)  Reviews: D. L. Boger, Tetrahedron, 39, 2869 (1983); M. Ohno, T. Sasaki, J. Syn. Org. Chem. Japan, 42, 125 (1984).

3)  Y.-S. Cheng, A. T. Lupo, Jr., F. W. Fowler, J. Am. Chem. Soc., 105, 7696 (1983).

4)  M. A. Whitesell, E. P. Kyba, Tetrahedron Lett., 25, 2119 (1984).

5)  All new compounds have been characterized by elemental analysis and/or high resolution mass spectra.  Characteristic data are recorded together with yield.  IR spectra were taken in $CHCl_3$ and NMR spectra in $CDCl_3$: (2a) 64% yield; mp 135 - 137°; NMR δ 10.00 (1H, s, CHO).  (2b) 75% yield; mp 143 - 144°; NMR δ 10.03 (1H, s, CHO).  (2c) 77% yield; mp 128 - 131°; NMR δ 9.93 (1H, s, CHO).  (2d) 65% yield; NMR δ 10.10 (1H, s, CHO).  (3a) 70% yield; mp 127 - 128°; IR ($CHCl_3$) $cm^{-1}$ 3450 (NH), 1700, 1670, 1630 (C=O); NMR δ 1.33 (3H, t, J = 7 Hz, $CH_2CH_3$), 2.95 (2H, t, J = 7 Hz, $ArCH_2$), 3.32 - 3.64 (2H, m, $CH_2N$), 3.87 (6H, s, 2 × OMe), 4.26 (2H, q, J = 7 Hz, $CH_2CH_3$), 6.26 (1H, d, J = 16 Hz, COCH=CH), 6.68 and 7.04 (each 1H, each s, 2 × ArH), 7.88 (1H, d, J = 16 Hz, ArCH=CH).  (3b) 88% yield; mp 133 - 134°; IR $cm^{-1}$ 3450 (NH), 1700, 1680, 1630 (C=O); NMR δ 1.33 (3H, t, J = 7 Hz, $CH_2CH_3$), 1.82 (3H, dd, J = 2 and 8 Hz, =$CHCH_3$), 2.94 (2H, t, J = 7 Hz, $ArCH_2$), 3.35 - 3.57 (2H, m, $CH_2N$), 3.84 and 3.89 (each 3H, each s, 2 × OMe), 4.24 (2H, q, J = 7 Hz, $CH_2CH_3$), 5.71 (1H, dd, J = 2 and 16 Hz, COCH=), 6.26 (1H, d, J = 16 Hz, COCH=), 6.69 (1H, s, ArH), 6.80 (1H, dq, J = 8 and 16 Hz, =$CHCH_3$), 7.04 (1H, s, ArH), 7.89 (1H, d, J = 16 Hz, ArCH=).  (3c) 73% yield; mp 151 - 153°; IR $cm^{-1}$ 3440 (NH), 1700, 1660, 1620 (C=O); NMR δ 1.31 (3H, t, J = 8 Hz, $CH_2CH_3$ ), 3.00 (2H, t, J = 7 Hz, $ArCH_2$), 3.46 - 3.65 (2H, m, $CH_2N$), 3.86 and 3.88 (each 3H, each s, 2 × OMe), 4.22 (2H, q, J = 8 Hz, $CH_2CH_3$), 6.25 and 6.29 (each 1H, each d, each J = 16 Hz, 2 × COCH=), 6.70 and 7.06 (each 1H, each s, 2 × ArH), 7.60 and 7.93 (each 1H, each d, each J = 16 Hz, 2 × CH=CHCO).  (3d) 74% yield; mp 123 - 125°;  IR $cm^{-1}$ 3450 (NH), 1700, 1660, 1628 (C=O); NMR δ 1.33 (3H, t, J = 8 Hz, $CH_2CH_3$), 1.70 (3H, br d, J = 8 Hz, $CH_3CH$=), 1.75 (3H, s, =C($CH_3$)-), 2.93 (2H, t, J = 8 Hz, $ArCH_2$), 3.30 - 3.63 (2H, m, $CH_2N$),

3.78 and 3.81 (each 3H, each s, 2 × OMe), 4.23 (2H, q, J = 8 Hz, C$\underline{H}_2$CH$_3$), 5.73 - 6.13 (2H, m, =C$\underline{H}$CH$_3$, NH), 6.46 (1H, d, J = 16 Hz, =CHCO), 6.65 and 7.00 (each 1H, each s, 2 × ArH), 7.83 (1H, d, J = 16 Hz, ArC$\underline{H}$=). (5a) 44% yield; IR cm$^{-1}$ 1720, 1620 (C=O); NMR δ 1.33 (3H, t, J = 7 Hz, CH$_2$C$\underline{H}_3$), 3.80 and 3.85 (each 3H, each s, 2 × OMe), 5.03 (1H, d, J = 8 Hz, 11b-H), 6.60 (2H, br s, 2 × ArH). (5b) 52% yield; mp 158 - 159°; IR cm$^{-1}$ 1730, 1630 (C=O); NMR δ 1.09 (3H, d, J = 7 Hz, 2-Me), 1.32 (3H, t, J = 8 Hz, CH$_2$C$\underline{H}_3$), 3.78 and 3.83 (each 3H, each s, 2 × OMe), 4.26 (2H, q, J = 8 Hz, C$\underline{H}_2$CH$_3$), 5.00 (1H, d, J = 8 Hz, 11b-H), 6.51 and 6.61 (each 1H, each s, 2 × ArH). (5c) 47% yield; mp 154 - 157°; IR cm$^{-1}$ 1725, 1630 (C=O); NMR δ 0.74 (3H, t, J = 8 Hz, CH$_2$C$\underline{H}_3$), 3.61 (2H, q, J = 8 Hz, C$\underline{H}_2$CH$_3$), 3.80 and 3.82 (each 3H, each s, 2 × OMe), 5.00 - 5.29 (2H, m, 11b-H, 6-H), 6.57 and 6.65 (each 1H, each s, 2 × ArH). (5d) 25% yield: IR cm$^{-1}$ 1730, 1625 (C=O); NMR δ 0.98 and 1.23 (each 3H, each d, each J = 7 Hz, 2 × Me), 1.35 (3H, t, J = 7 Hz, CH$_2$C$\underline{H}_3$), 3.76 and 3.84 (each 3H, each s, 2 × OMe), 4.50 (2H, q, J = 7 Hz, C$\underline{H}_2$CH$_3$), 5.04 (1H, d, J = 9 Hz, 11b-H), 6.43 and 6.61 (each 1H, each s, 2 × ArH). (5e) 41% yield: mp 166 - 168°; IR cm$^{-1}$ 1730, 1625 (C=O); NMR δ 0.88 (3H, t, J = 7 Hz, CH$_2$C$\underline{H}_3$), 1.15 and 1.32 (each 3H, each d, each J = 7 Hz, 2 × Me), 3.80 and 3.83 (each 3H, each s, 2 × OMe), 4.68 - 5.16 (2H, m, 11b-H, 6-H), 6.56 and 6.63 (each 1H, each s, 2 × ArH). (6) 62% yield from the β-carboline; mp 194 - 195°; IR cm$^{-1}$ 3475 - 3460 (2 × NH), 1700, 1682, 1632 (C=O); NMR δ 1.34 (3H, t, J = 6 Hz, CH$_2$C$\underline{H}_3$), 1.79 (3H, dd, J = 2 and 5.8 Hz, =CHC$\underline{H}_3$), 3.14 (2H, t, J= 5.7 Hz, ArCH$_2$), 3.43 - 3.69 (2H, m, CH$_2$N), 4.25 (2H, q, J = 6 Hz, C$\underline{H}_2$CH$_3$), 5.66 (1H, dd, J = 2 and 16 Hz, COCH=), 6.17 (1H, d, J = 16 Hz, COC$\underline{H}$=), 6.81 (1H, dq, J = 16 and 5.8 Hz, =C$\underline{H}$CH$_3$), 7.71 (1H, d, J = 16 Hz, ArC$\underline{H}$=), 8.42 (1H, br s, NH). (7) 58% yield; IR cm$^{-1}$ 3453 (NH), 1710, 1630 (C=O); NMR δ 1.04 (3H, d, J = 5 Hz, 2-Me), 1.39 (3H, t, J = 6 Hz, CH$_2$C$\underline{H}_3$), 4.39 (2H, q, J = 6 Hz, C$\underline{H}_2$CH$_3$), 4.98 - 5.27 (2H, m, 12b-H, 6-H), 8.17 (1H, br s, NH).

6) S. Danishefsky, T. Kitahara, <u>J. Am. Chem. Soc.</u>, 96, 7807 (1974).

7) M. Ihara, M. Toyota, K. Fukumoto, T. Kametani, <u>Tetrahedron Lett.</u>, 25, 2167 (1984).

8) The preferred formation of 5b-e and 7 could also be understood by the secondary orbital effect.