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INTRAMOLECULAR DIELS-ALDER REACTION OF 3-(1H-INDOL-3-YL)-2-PROPENOATES: SYNTHESIS OF FUSED INDOLE COMPOUNDS

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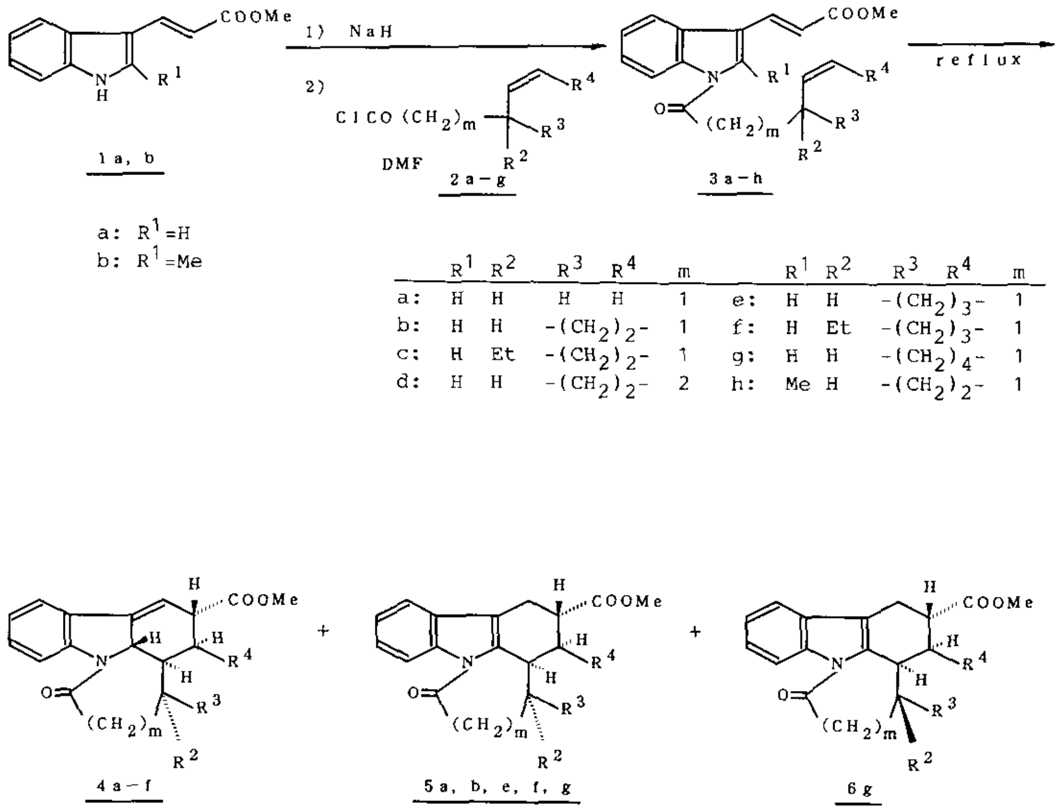
Abstract - Intramolecular Diels-Alder reaction of 3-(1H-indol-3-yl)-2-propenoates having the olefinic substituents at the 1-position of the indole ring gave stereoselectively fused indole compounds.

There have been many reports about the intermolecular Diels-Alder reaction of 3-vinylindoles.[1,2] Recently, U. Pindur reviewed the intermolecular Diels-Alder reaction of 1- or 2-vinylindoles.[3] However, very little is known about the intramolecular Diels-Alder reaction of 3-(1H-indol-3-yl)-2-propenoates.[4] There are many naturally occurring fused indole compounds such as vinca alkaloids. Here, we report on the facile stereoselective synthesis of fused indole compounds using intramolecular Diels-Alder reaction of (**E**)- and (**Z**)-3-(1H-indol-3-yl)-2-propenoates (**3a**-**h** and **9a**-**c**) having olefinic substituents at the 1-position of the indole ring.

The (**E**)-propenoates **3a**-**h** were prepared by acylation of methyl (**E**)-3-(1H-indol-3-yl)-2-propenoates (**1a,b**) with compounds (**2a-g**).

Intramolecular Diels-Alder reaction of **3a-h** was carried out under reflux in the appropriate solvent to indolines (**4a**-**f**,**7**,**8**) and indoles (**5a,b,e-g,6g**) shown in Scheme 1. The ratio of products depended on the reaction temperature, the number of m, R^3 and R^4. The results are shown in Table 1.

Reaction of **3a** under reflux in mesitylene afforded only the **4a** in 77.6% yield (Run 1). On the other hand reflux of **3a** in o-dichlorobenzene gave predominantly indole **5a** (Run 2). Because the indole type product **5a** is thermodynamically more stable than the indoline type product **4a**, the reaction in o-dichlorobenzene which has a higher boiling point than mesitylene seems to give **5a** predominantly.



a: R^1=H
b: R^1=Me

	R^1	R^2	R^3	R^4	m		R^1	R^2	R^3	R^4	m
a:	H	H	H	H	1	e:	H	H	$-(CH_2)_3-$		1
b:	H	H	$-(CH_2)_2-$		1	f:	H	Et	$-(CH_2)_3-$		1
c:	H	Et	$-(CH_2)_2-$		1	g:	H	H	$-(CH_2)_4-$		1
d:	H	H	$-(CH_2)_2-$		2	h:	Me	H	$-(CH_2)_2-$		1

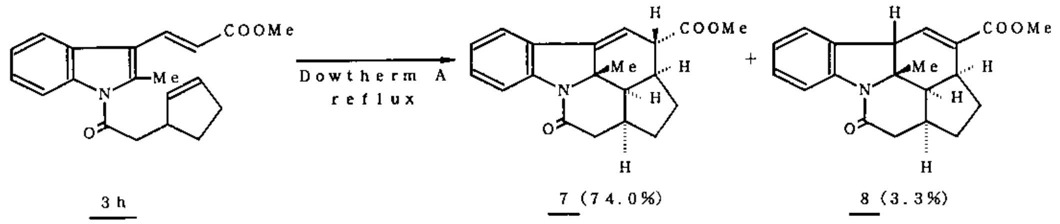
	R^2	R^3	R^4	m
a:	H	H	H	1
b:	H	$-(CH_2)_2-$		1
c:	Et	$-(CH_2)_2-$		1
d:	H	$-(CH_2)_2-$		2
e:	H	$-(CH_2)_3-$		1
f:	Et	$-(CH_2)_3-$		1

	R^2	R^3	R^4	m
a:	H	H	H	1
b:	H	$-(CH_2)_2-$		1
e:	H	$-(CH_2)_3-$		1
f:	Et	$-(CH_2)_3-$		1
g:	H	$-(CH_2)_4-$		1

	R^2	R^3	R^4	m
g:	H	$-(CH_2)_4-$		1

Scheme 1.

Diels-Alder reaction of **3b,c,d,f** under reflux in mesitylene gave only **4b,c,d,f** respectively (Runs 3, 4, 5, 7). However, **3e** afforded a mixture of **4e** and **5e** in 62.5 and 11.5 % yields, respetively (Run 6). On the other hand, cyclization of **3g** afforded **5g** and its epimer **6g** in 21.7 and 58.3% yields, respectively (Run 8). Cyclization of **3h** gave **7** and double bond migrated product **8** under reflux in Dowtherm A in 74.0 and 3.3 % yields, respectively, but the reaction did not proceed under reflux in mesitylene.

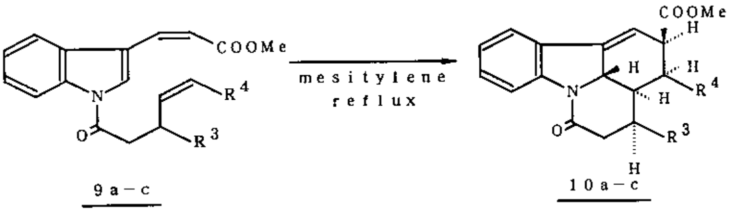


Scheme 2.

Table 1. Results of Intramolecular Diels-Alder Reaction

Run	Starting Compd	R^2	R^3	R^4	m	solvent	reation time(hr.)	Yield(%) **4**	**5**	**6**
1	3a	H	H	H	1	mesitylene	20	77.6	trace	-
2	3a	H	H	H	1	o-dichlorobenzene	18	6.6	75.6	-
3	3b	H	$-(CH_2)_2-$		1	mesitylene	4	91.2	-	-
4	3c	Et	$-(CH_2)_2-$		1	mesitylene	4	96.4	-	-
5	3d	H	$-(CH_2)_2-$		2	mesitylene	30	56.5	-	-
6	3e	H	$-(CH_2)_3-$		1	mesitylene	15	62.5	11.5	-
7	3f	Et	$-(CH_2)_3-$		1	mesitylene	20	74.5	trace	-
8	3g	H	$-(CH_2)_4-$		1	mesitylene	14	-	21.7	58.3

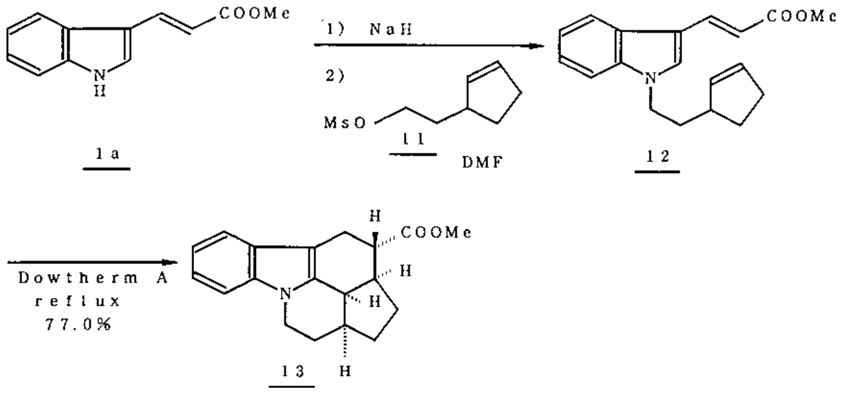
Cyclization of methyl (Z)-isomers (**9a-c**) gave **10a-c** under reflux in mesitylene, but the cyclization reaction was slower than in the case of the coresponding (**E**)-isomers (**3a,b,e**).



	R3	R4	Yield(%)
a:	H	H	47.0
b:	$-(CH_2)_2-$		86.9
c:	$-(CH_2)_3-$		20.3

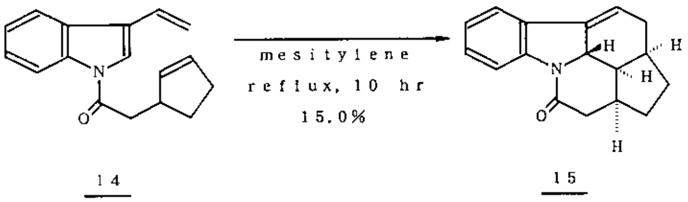
Scheme 3.

Diels-Alder reaction of **12** prepared by alkylation of 3-(1H-indol-3-yl)-2-propenoate (**1a**) with the mesylate (**11**) in DMF gave **13** under reflux in Dowtherm A, but this reaction also did not proceed in mesitylene under reflux.



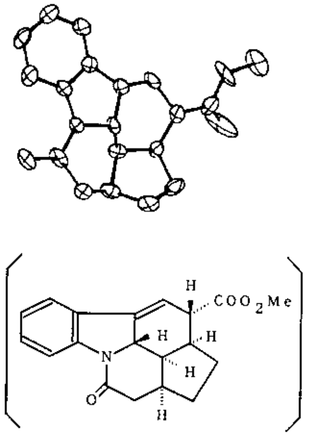
Scheme 4.

Cyclization of **14** required a longer reaction time than the corresponding propenoate (**3b**) and gave the product (**15**) in only 15% yield. Therefore, cyclization of 1-acylated 3-(1H-indol-3-yl)-2-propenoates (**3**) is an inverse electron-demand Diels-Alder reaction.[5]

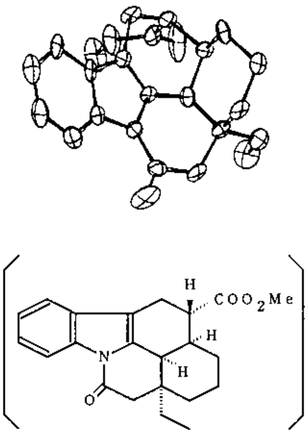


Scheme 5.

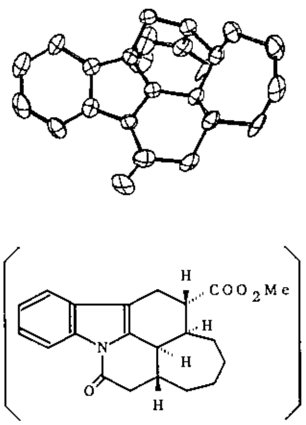
The structures of **4b** ,**5f** and **6g** were determined by the X-ray analyses.[8]



4b



5f



6g

In summary, we have developed a new method for stereoselective synthesis of fused indole compounds using intramolecular Diels-Alder reactions. Some of these fused indole compounds showed interesting pharmacological activity such as diuretic activity which will be reported elsewhere.

ACKNOWLEDGEMENTS

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4. After we presented the study of these reactions in the 107th Annual Meeting of the Pharmaceutical Society of Japan [Y. Shimoji, F. Saito, M. Kataoka, Y. Morisawa, K. Tomita, Y. Mizuno,and H. Koike, Abstract of the 107th Annual Meeting of the Pharmaceutical Society of Japan, p. 469 (1987)] and Patent [Eur. Pat. Appl. EP 187,619 (Sankyo Co.,LTD.,) 1986; Chem. Abstr., 1986, **105**, 152947p], M. K. Eberle, M. J. Shapiro and R. Stucki reported a similar reaction [M. K. Eberle, M. J. Shapiro,and R. Stucki, J. Org. Chem., 1987, **52**, 4661].
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6. All new compounds were chracterized by elemental analyses and spectral data. The physical and spectral data are as follows. **4a:** mp 182-184 °C. **4b:** mp 154-156 °C; ir (KBr) 1730 (C=O) and 1665 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.35-3.00 (10H, m), 3.80 (3H, s), 3.90 (1H, dt, J=11, 3 Hz), 6.13 (1H, t, J=3 Hz), 6.94-7.55 (3H, m), 8.03 (1H, d, J=8 Hz); ms (m/z) 309 (M^+). **4c:** mp 129-131 °C. **4d:** mp 152-155 °C; ir (KBr) 1740 (C=O) and 1670 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.48-2.97 (12H, m), 1.80 (3H, s), 4.30 (1H, dt, J=11, 3 Hz), 6.15 (1H, t, J=3 Hz), 6.90-7.48 (3H, m), 8.32 (1H, d, J=8 Hz); ms (m/z) 323 (M^+). **4e:** mp 172-175 °C; ir (KBr) 1730 (C=O) and 1650 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.15-3.00 (9H, m), 3.07 (1H, t, J=3 Hz), 3.71 (3H, s), 4.68 (1H, dt, J=10, 3 Hz), 5.86 (1H, t, J=3 Hz), 6.95-7.53 (3H, m), 8.15 (1H, d, J=8 Hz); ms (m/z) 323 (M^+). **4f:** mp 120-122 °C. **5a:** mp 157-159 °C. **5b:** mp 124-126 °C; ir (KBr) 1730 (C=O) and 1700 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.80-2.10 (4H, m), 2.37-3.33 (6H, m), 3.72 (3H, s), 7.20-7.55 (3H, m), 8.30-8.50 (1H, m); ms (m/z) 309

(M^+). **5e:** mp 156-158 °C; ir (KBr) 1730 (C=O) and 1695 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.80-1.80 (6H, m), 2.20 (1H, br), 2.40-3.37 (7H, m), 3.80 (1H, s), 7.15-7.50 (3H, m), 8.30-8.60 (1H, m); ms (m/z) 323(M^+). **5g:** mp 194-196 °C; ir (KBr) 1730 (C=O) and 1695 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.22-2.05 (8H, m), 2.38-3.46 (8H, m), 3.68 (3H, s), 7.15-7.58 (3H, m), 8.28-8.52 (1H, m); ms (m/z) 337 (M^+). **6g:** mp 160-161 °C; ir (KBr) 1722 (C=O) and 1700 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.05-2.20 (9H, m), 2.45-3.37 (7H, m), 3.62 (3H, s), 7.15-7.58 (3H, m), 8.25-8.50 (1H, m); ms (m/z) 337 (M^+). **7:** mp 139-141 °C. **10a:** mp 163.5-165 °C; ir (KBr) 1738 (C=O) and 1645 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.55-2.38 (5H, m), 2.50-2.75 (2H, m), 3.57 (1H, m), 3.77 (1H, s), 4.12 (1H, m), 5.87 (1H, t, J=4 Hz), 6.93-7.50 (3H, m), 8.10 (1H, d, J=8 Hz); ms (m/z) 283 (M^+). **10b:** mp 186-188 °C. **10c:** mp 185-190 °C. **13:** mp 91-92 °C; ir (KBr) 1720 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.90-3.10 (11H, m), 3.30 (1H, t, J=8 Hz), 3.70 (3H, s), 3.60-4.20 (2H, m), 6.95-7.34 (3H, m), 7.38-7.60 (1H, m); ms (m/z) 295 (M^+). **15:** mp 157-159 °C; ir (KBr) 1670 (C=O) cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.03-3.05 (10H, m), 3.98 (1H, ddd, J=11, 4, 4 Hz), 6.02 (1H, m), 6.93-7.54 (3H, m), 8.11 (1H, d, J=8 Hz); ms (m/z) 251 (M^+).

7. The transformation from **4b** to **5b** was performed in the presence of caralysts as follows:

   1) Wilkinson's catalyst in xylene under reflux, 88.6% yield;
   2) 10% Pd on C in xylene under reflux, 98% yield;
   3) 5% Rh on C in xylene under reflux, 32% yield;
   4) HCl in methanol under reflux, 100% yield.

8. Crystal date of **4b:** $C_{19}H_{19}NO_3$=309.4, monoclinic, $P2_1/c$, a=13.860(6), b=6.935(7), c=16.841(5)Å, β=111.38(3)°, U=1507.5$Å^3$, Z=4, Dc=1.36g.cm^{-3}, R=0.083; **5f:** $C_{22}H_{25}NO_3$=351.4, monoclinic, $p2_1/a$, a=8.781(2), b=21.886(6), c=9.680(2)Å, β=74.662(2)°, U=1790.4$Å^3$, Z=4, Dc=1.30g.cm^{-3}, R=0.097; **6g:** $C_{21}H_{23}NO_3$=337.4, monoclinic, $p2_1/n$, a=8.020(1), b=17.311(3), c=12.510(1)Å, β=98.16(1)°, U=1719.4$Å^3$, Z=4, Dc=1.30g.cm^{-3}, R=0.067.

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