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The gramine route to the Diels–Alder adducts of indolo-2,3-quinodimethanes

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Abstract

Indolo-2,3-quinodimethanes were smoothly generated by thermal fragmentation of 2-substituted 3-aminomethylindoles, and engaged in Diels–Alder reactions yielding 1,2,3,4-tetrahydrocarbazoles with a large array of possible substituents at either position. An intramolecular variant of the procedure generated a tetracyclic (unnatural) indolomonoterpene with complete control of three stereocenters. © 1999 Elsevier Science Ltd. All rights reserved.

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The preceding paper[1] reports on the easy generation of indolo-2,3-quinodimethane **2** (Scheme 1) through thermal expulsion of dimethylamine from gramine **1**. A preliminary study of the Diels–Alder reactivity of **2**, and its extension to the synthesis of variously substituted indolo-2,3-quinodimethanes (IQDMs) is presented hereafter.

Refluxing gramine **1** with *N*-phenylmaleimide in toluene for 2 h yielded the unique tetrahydrocarbazole **3**[2] (100%) whose relative configuration resulted from the *endo* approach of the dienophile and from the favored *Z* configuration of the reacting anilinoacrylic ester **2**. Under similar conditions, dimethyl maleate gave the two triesters **4a** (25%) and **4b** (32%), by analogy with similar reactions of other heteroquinodimethanes.[3] The reaction of methyl acrylate was regiospecific but not stereospecific, affording **5a** (34%) and **5b** (43%). The regiospecificity agrees with the distribution of electron densities,[4] while isolation of the two epimers is ascribed to some *exo* approach, rather than to epimerization. Indeed, methyl methacrylate, similarly, gave the two epimers **6a** and **6b** (31% versus 18%).[5] Generation of **2** in the presence of *p*-benzoquinone, resulted in overoxidation of the adduct by the quinone to the indolo[2,3-*e*]naphthoquinone **7** (49%).[6]

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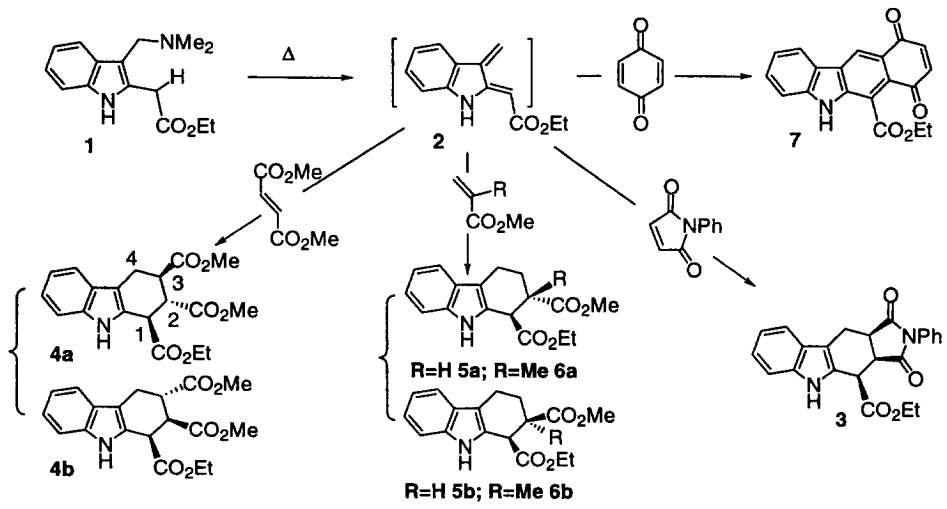
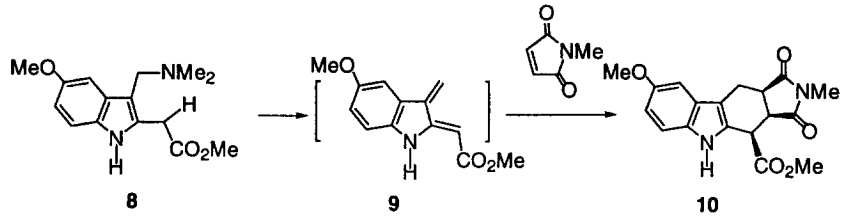


Scheme 1.

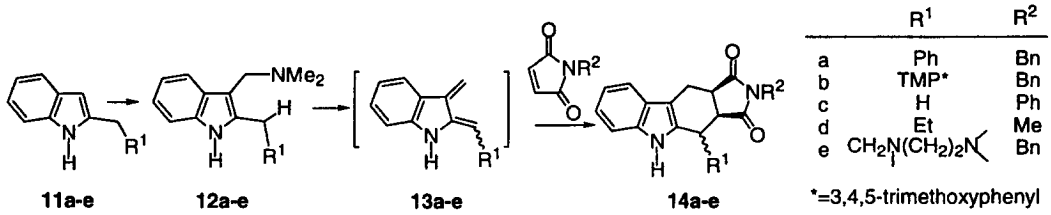
Gramine **8** (Scheme 2) was prepared from the related 5-methoxyindole-2-acetate,[7] and reacted with *N*-methylmaleimide to yield the 6-methoxytetrahydrocarbazole **10** (61%),[8] via the intermediate IQDM **9**.



Scheme 2.

Activation of the 2-methylene in the form of an acetic ester was subsequently proven not to be mandatory, thus notably extending the scope of the reaction. Thus, 2-benzylindole **11a** (Scheme 3) was transformed into gramine **12a** (61%), and reacted with *N*-benzylmaleimide to yield **14a** (43%).[9] Similarly, 2-trimethoxybenzylindole **11b** gave **14b** (75%) via gramine **12b**. Still more interesting was the obtention of the tetrahydrocarbazoles **14c**[10] (56%) and **14d**[11] (70%) from the 2-alkylindoles **11c** and **11d** through the gramines **12c,d** and the derived IQDMs **13c,d**, respectively. In particular, obtention of **14d** showed that IQDM **13d** did not rearrange to a 2-vinylindole prior to electrocyclization. For pharmacological purposes, indole **11e** was prepared through $LiAlH_4$ reduction of the amide obtained from **24a** and *N,N,N'*-trimethylethylene diamine, and similarly transformed into gramine **12e**, and thence to IQDM **13e** and to tetrahydrocarbazole **14e** (40%).[12] This last result emphasizes the importance of obtaining an IQDM thermally from a gramine without the necessity of a quaternization.

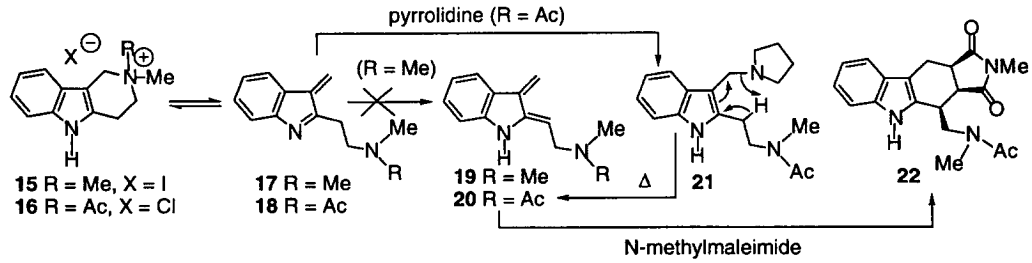
In an unsuccessful attempt to generate the aminomethyl-IQDM **19** (Scheme 4), the *N,N*-dimethyltetrahydro-ɣ-carbolinium salt **15** was heated with *N*-methylmaleimide, yielding no Diels–Alder adduct. Nor did the *N*-acylium derivative **16** obtained from *N*-methyltetrahydro-ɣ-carboline and acetyl chloride give Diels–Alder adducts, which indicated that the 3-methylene-3-*H* indoles **17** and **18**, if formed, readily recyclize to **15** and **16**, rather than equilibrating to the IQDMs **19** and **20**. However, treatment of **16** with pyrrolidine gave the gramine **21** whose reaction with *N*-methylmaleimide in



	R^1	R^2
a	Ph	Bn
b	TMP*	Bn
c	H	Ph
d	Et	Me
e	$CH_2N(CH_2)_2N$	Bn

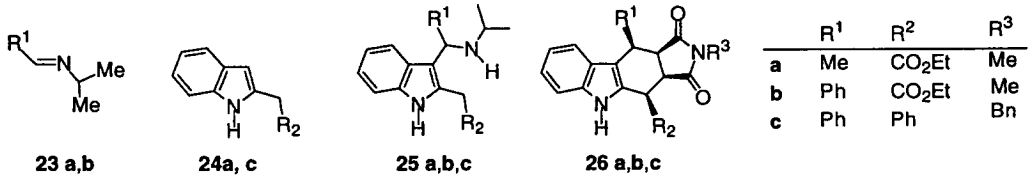
Scheme 3.

refluxing 1,2-dichlorobenzene afforded the tetrahydrocarbazole **22** (74%).[13] This result obviously confirms the direct formation of an IQDM via a [1,5]-sigmatropic process.



Scheme 4.

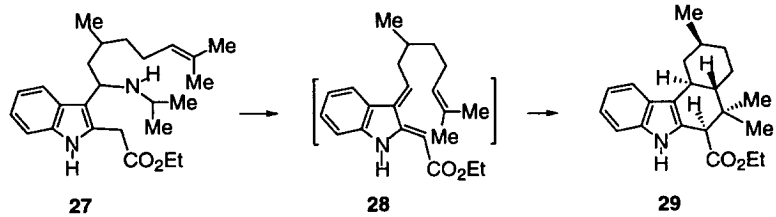
Having thus obtained access to IQDMs with variously substituted 2-methylenes, we next turned to the introduction of substituents on the 3-methylene group. While preparation of gramines from indoles and Mannich reagents derived from aldehydes and dialkylamines only works well with formaldehyde, isopropylaldimines are known[14] to react much more efficiently.



	R^1	R^2	R^3
a	Me	CO_2Et	Me
b	Ph	CO_2Et	Me
c	Ph	Ph	Bn

Thus, imine **23a** was prepared from acetaldehyde and isopropylamine, and further reacted with **24a** to give the gramine **25a**, whose reaction with *N*-methylmaleimide in refluxing toluene afforded **26a** (100%). Similarly, the benzylideneimine **23b** gave the gramine **25b**, whose reaction with *N*-methylmaleimide gave **26b** (96%). Moreover, preparation of the imine proved to be unnecessary, as reacting an equimolar mixture of **24a**, benzaldehyde, and *N*-methylmaleimide in toluene also produced **25b** with a 74% yield. As an example of a synthesis implicating an IQDM substituted at the two termini of the diene, the benzylideneimine **23b** was reacted with **24c** to give the gramine **25c**, whose reaction with *N*-benzylmaleimide gave the diphenyltetrahydrocarbazole **26c** (55%).[15]

The versatility of the gramine route to IQDMs was further exemplified by its application to an intramolecular Diels–Alder reaction.



Refluxing (toluene, 2 h) the gramine **27** obtained from **24a** and from the isopropylimine of (±)-citronellal afforded the tetracyclic derivative **29** (34%) via the IQDM **28**. Interestingly enough, **29** was isolated as a unique product, demonstrating the stereo control of the three newly created chiral centers. The relative configurations of the stereocenters in **29** could not be simply deduced from the NMR spectra, and are tentatively assigned as depicted in the formula: from the probable configurations of the double bonds in **28**, H-1 and H-4 (carbazole numbering) have to be *cis* in **29**, and *trans* to H-3. It is presumed that the dimethyl alkene portion of the molecule will cyclize from the side resulting in an equatorial orientation of the secondary methyl group.

We have thus developed a novel versatile procedure allowing the smooth generation of various highly reactive IQDM's, from easily accessible starting materials, and under relatively mild thermal conditions.

References

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2. General procedure: A solution of **1** (0.5 mmol) and *N*-phenylmaleimide (2 mmol) in toluene (10 ml), was refluxed for 2 h. After evaporation under reduced pressure, the residue was chromatographed (cyclohexane:ethyl acetate, 4:1) on a column of silica gel to give **3** (100%). Compound **3**: MS: 388 ($M^{+\bullet}$, 87), 342 (73), 315 (37), 215 (12), 194 (16), 168 (100). ^{1}H NMR ($CDCl_3$) δ: 1.22 (t, *J*=6.7 Hz, 3H), 3.30 (m, 2H), 3.56 (m, 1H), 3.82 (dd, *J*=9.0 and 6.7 Hz, 1H), 4.18 (m, 2H), 4.28 (d, *J*=6.7 Hz, 1H), 7.07–7.20 (m, 4H), 7.30–7.40 (m, 4H), 7.52 (d, *J*=8.0 Hz, 1H), 9.11 (s, NH, 1H). ^{13}C NMR ($CDCl_3$) δ: 13.4, 19.9, 39.6, 40.1, 42.6, 61.5, 109.2, 111.1, 117.5, 119.1, 121.6, 125.6, 126.3, 128.3, 128.6, 128.7, 131.5, 135.8, 169.8, 177.4, 179.
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5. The respective structures were not attributed.
6. Compound **7**: MS: 319 ($M^{+\bullet}$, 47), 273 (100). ^{1}H NMR (DMSO-d_6) δ: 1.42 (t, *J*=7.0 Hz, 3H), 4.54 (q, *J*=7.0 Hz, 2H), 7.00 and 7.06 (2d, *J*=11.2 Hz, 2H), 7.32 (t, *J*=8.0 Hz, 1H), 7.60 (m, 2H), 8.40 (d, *J*=8.0 Hz, 1H), 8.86 (s, 1H), 12.25 (s, NH, 1H). ^{13}C NMR (DMSO-d_6) δ: 13.9, 61.8, 112.3, 117.1, 120.5, 121.0, 122.1, 123.3, 125.4, 126.7, 128.8, 138.5, 138.8, 139.2, 142.2, 148.2, 167.0, 184.1, 184.7.
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8. Compound **10**: MS: 356 ($M^{+\cdot}$, 78), 342 (42), 310 (84), 198 (72), 182 (44), 167 (46), 149 (61), 111 (100). ^{1}H NMR ($CDCl_3$) δ: 2.87 (s, 3H), 3.05 (s, 3H), 3.30–3.50 (m, 3H), 3.85 (s, 3H), 4.10–4.30 (m, 2H), 6.80 (m, 1H), 6.94 (s, 1H), 7.22 (d, *J*=9.0 Hz, 1H), 9.22 (s, 1H).
9. Compound **14a**: MS: 406 ($M^{+\cdot}$, 100), 315 (14), 244 (74), 218 (99), 167 (25). ^{1}H NMR ($CDCl_3$) δ: 3.08 (m, 1H), 3.42 (m, 2H), 3.56 (dd, *J*=9.0 and 3.0 Hz, 1H), 4.56 (s, 2H), 4.87 (d, *J*=3.0 Hz, 1H), 6.94 (m, 3H), 7.20 (m, 5H), 7.27 (m, 5H), 7.57 (d, *J*=7.2 Hz, 1H), 8.00 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.3, 39.4, 39.5, 42.4, 48.8, 108.3, 111.1, 118.2, 119.8, 122.0, 126.5, 127.2, 127.3, 127.4, 128.4, 128.6, 129.0, 132.9, 135.0, 135.8, 140.5, 178.6, 179.6.
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11. Compound **14d**: MS: 282 ($M^{+\cdot}$, 72), 253 (65), 168 (100), 156 (31). ^{1}H NMR ($CDCl_3$) δ: 1.04 (t, *J*=7.3 Hz, 3H), 1.73 (m, 1H), 2.02 (m, 1H), 2.88 (s, 3H), 3.10–3.23 (m, 3H), 3.38 (m, 2H), 7.12 (m, 2H), 7.31 (d, *J*=7.0 Hz, 1H), 7.53 (d, *J*=7.0 Hz, 1H), 8.24 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 12.3, 20.0, 21.7, 24.7, 36.6, 40.5, 44.1, 107.4, 110.9, 117.7, 119.6, 121.3, 126.6, 135.3, 136.0, 177.8, 179.9.
12. Compound **14e**: UV: 226, 274, 283, 292. IR: 1700, 2805, 2945, 3030. MS: 444 ($M^{+\cdot}$, 10), 400 (8), 386 (37), 343 (18), 182 (20), 168 (26). ^{1}H NMR ($CDCl_3$) δ: 2.24 (dt, *J*=5.6 and 3.3 Hz, 1H), 2.30 (s, 3H), 2.37 (s, 6H), 2.43 (dt, *J*=15.6 and 3.2 Hz, 1H), 2.50 (dd, *J*=12.8 and 3.2, 1H), 2.78 (m, 1H), 2.83 (m, 1H), 2.94 (td, *J*=11.2 and 4.9 Hz, 1H), 3.25 (dd, *J*=8.4 and 5.2 Hz, 1H), 3.43 (m, 2H), 3.48 (dd, *J*=15.1 and 1.5 Hz, 1H), 3.67 (t, *J*=12.5 Hz, 1H), 4.43 (AB, *J*=14.8 Hz, 2H), 6.55 (d, *J*=7.5 Hz, 2H), 6.81 (t, *J*=7.5 Hz, 2H), 6.98 (t, *J*=7.5 Hz, 1H), 7.04 (t, *J*=7.9 Hz, 1H), 7.11 (t, *J*=7.9 Hz, 1H), 7.29 (d, *J*=7.9 Hz, 1H), 7.47 (d, *J*=7.9 Hz, 1H), 12.27 (s, 1H). ^{13}C NMR ($CDCl_3$) δ: 21.9, 32.9, 41.7, 42.0, 43.2, 44.0, 44.1, 54.1, 55.1, 55.6, 106.1, 111.3, 117.5, 118.7, 120.3, 126.2, 126.7, 127, 128.2, 134.9, 135.9, 136, 177.4, 179.6.
13. Compound **22**: MS: 339 ($M^{+\cdot}$, 6), 266 (100), 253 (10), 229 (7), 180 (11), 168 (55). ^{1}H NMR ($CDCl_3$) δ: 2.20 (s, 3H), 2.90 (m, 6H), 3.27 (m, 2H), 3.40–3.60 (m, 3H), 3.73 (m, 1H), 4.08 (m, 1H), 7.20 (m, 2H), 7.34 (d, *J*=7.6 Hz, 1H), 7.53 (d,

J=7.6 Hz, 1H), 9.47 (s, 1H).^{13}C NMR ($CDCl_3$) δ: 21.0, 21.9, 25.1, 33.8, 36.9, 39.7, 43.2, 50.4, 107.8, 111.2, 117.9, 119.5, 121.6, 126.4, 132.8, 135.7, 172.1, 179.5, 179.8.

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15. Compound **26c**: MS: 482 ($M^{+\cdot}$, 100), 405 (13), 320 (25), 295 (40), 278 (14), 244 (22), 218 (20), 206 (18), 167 (7). ^{1}H NMR (DMSO-d_6) δ: 3.21 (t, J=11.0 Hz, 1H), 3.97 (dd, J=11.0 and 4.5 Hz, 1H), 4.45 (2d, J=16.0 Hz, 2H), 4.74 (d, J=11.0 Hz, 1H), 5.04 (d, J=4.0 Hz, 1H), 6.91 (m, 1H), 7.04 (m, 3H), 7.14–7.23 (m, 5H), 7.30–7.46 (m, 10H), 10.34 (s, 1H). ^{13}C NMR (CD_3OD) δ: 41.6, 45.8, 47.6, 50.0, 54.1, 116.6, 116.9, 123.0, 123.9, 126.3, 130.8, 132.0, 132.2, 132.4, 132.7, 133.2, 133.5, 133.6, 134.1, 134.9, 141.3, 142.2, 143.0, 144.8, 146.1, 179.2, 179.8.