JOC Article

Aromatic Bromination versus Oxidation of Indolylmalonates by Bromine

Martha S. Morales-Ríos, Norma F. Santos-Sánchez, Oscar R. Suárez-Castillo, and Pedro Joseph-Nathan*

Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, México D. F. 07000, Mexico

pjoseph@nathan.chem.cinvestav.mx

Received August 15, 2002

The reactions of 5-substituted indolylmalonates (**2a**−**e**), carrying an electron-withdrawing group at the N(1) position, with bromine in CCl_4 or AcOH are reported. These substrates undergo oxidation in competition with the well-known aromatic bromination. Under the two sets of conditions, with parent indolylmalonate (**2a**), chemospecific oxidation is observed, whereas with 5-hydroxyindolylmalonate (**2c**), bromination at the 4- and 6-position is the dominating reaction. Investigation of the products composition of several 5-substituted indolylmalonates revealed the following trend: with a 5-substituted electron-withdrawing group like fluorine, the indolylmalonate undergoes oxidation rather than bromination. In contrast, with a 5-substituted electron-donating group, like a hydroxyl group, the ring bromination occurs preferentially over the oxidation. When the 5-substituent is an alkoxyl group, a significant amount of brominated-oxidized products is obtained. Monitoring the oxidation reaction by mass spectrometry allowed the characterization of the 2-bromoindolylidenemalonate intermediate. A bromonium ion is considered as possible pathway in the formation of this intermediate. The conformation of unsymmetrical methoxyl and benzyloxyl substituents was determined from ^{1}H NMR spectra, single-crystal X-ray diffraction and ab initio calculations.

Introduction

In the past decades, many brominated indole derivatives possessing diverse structural complexity have been isolated from a variety of marine sources, and as a result, pharmacological studies using these marine natural products are increasing in number and scope.[1] One of the most famous brominated indole marine natural product is tyrian purple isolated from a marine mollusk.[2] Other brominated indoles with important biological activities are 5-bromo-*N*,*N*-dimethyltryptamine, isolated from a marine sponge,[3] and the brominated physostigmine alkaloids isolated from a cheilostome bryozoan.[4]

In the course of our research on 2-hydroxyindolenines, as intermediates for the synthesis of bioactive brominated physostigmine alkaloids,[5] we have shown that the oxidation of 3-indolylcyanoacetates with HNO_3 or CrO_3 yields stable 2-hydroxyindolenines[6] that could be converted to the corresponding indole alkaloids.[5] Although oxidation of the 2,3 indole double bond, which is essential under the influence of the substituents in the 1-, 2-, or 3-positions,[7a] has been carried out with a great variety of agents, such as bromine,[7b,c] NBS,[7d,e] MoO_5−HMPA,[7f] thallium trinitrate,[7g] *t*-BuOCl,[7h] SO_2Cl_2,[7i] lead tetraacetate,[7j] and more recently with *m*-CPBA,[8a] CF_3CO_2H,[8b] and OsO_4−pyridine,[8c] this is limited in most cases to the indol-2- and 3-one formation.

From the point of creating new biologically brominated active compounds based on indolenine chemistry, we

† To whom correspondence should be addressed. Phone: (5255) 5747-7112. Fax: (5255) 5747-7137.

(1) Reviews: (a) Faulkner, D. J. *J. Nat. Prod. Rep*. **1984**, *1*, 551−598. (b) Faulkner, D. J. *J. Nat. Prod. Rep*. **1986**, *3*, 1−33. (c) Faulkner, D. J. *J. Nat. Prod. Rep*. **1987**, *4*, 539−576. (d) Faulkner, D. J. *J. Nat. Prod. Rep*. **1988**, *5*, 613−663. (e) Faulkner, D. J. *J. Nat. Prod. Rep*. **1990**, *7*, 269−309. (f) Faulkner, D. J. *J. Nat. Prod. Rep*. **1991**, *8*, 97−147. (g) Faulkner, D. J. *J. Nat. Prod. Rep*. **1992**, *9*, 323−364. (h) Saxton, J. E. *J. Nat. Prod. Rep*. **1994**, *11*, 493−531. (i) Faulkner, D. J. *J. Nat. Prod. Rep*. **1995**, *12*, 223−270. (j) Ihara, M.; Fukumoto, K. *J. Nat. Prod. Rep*. **1995**, *12*, 277−301. (k) Faulkner, D. J. *J. Nat. Prod. Rep*. **1996**, *13*, 75−125. (l) Faulkner, D. J. *J. Nat. Prod. Rep*. **2001**, *18*, 1−49.

(2) (a) Bergman, J.; Koch, E.; Pelcman, B. *Tetrahedron*, **1995**, *51*, 5631−5642. (b) Butler, A.; Walker, J. V. *Chem. Rev*. **1993**, *93*, 1937−1944.

(3) Djura, P.; Stierle, D. B.; Faulkner, D. J.; Arnold, E.; Clardy, J. *J. Org. Chem*. **1980**, *45*, 1435−1441.

(4) For a review, see: Christophersen, C. *Acta Chem. Scand. B* **1985**, *39*, 517−529.

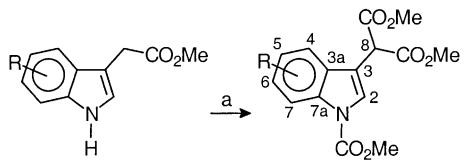
(5) (a) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Joseph-Nathan, P. *J. Org. Chem*. **1999**, *64*, 1086−1087. (b) Morales-Ríos, M. S.; Suárez-Castillo, O. R.; Trujillo-Serrato, J. J.; Joseph-Nathan, P. *J. Org. Chem*. **2001**, *66*, 1186−1192.

(6) (a) Morales-Ríos, M. S.; Bucio, M. A.; Joseph-Nathan, P. *J. Heterocycl. Chem*. **1993**, *30*, 953−956. (b) Morales-Ríos, M. S.; Bucio, M. A.; Joseph-Nathan, P. *Magn. Reson. Chem*. **1993**, *31*, 960−962. (c) Morales-Ríos, M. S.; Martínez-Galero, N. X.; Loeza-Coria, M.; Joseph-Nathan, P. *J. Org. Chem*. **1995**, *60*, 6194−6197.

(7) For reviews, see: (a) Karp, G. M. *Org. Prep. Proced. Int*. **1993**, *25*, 481−513. (b) Dmitrenko, G. I.; Gross, E. A.; Vice, S. F. *Can. J. Chem*., **1980**, *58*, 808−813. (c) Hino, T.; Nakagawa, M.; Akaboshi, S. *Chem. Pharm. Bull*. **1967**, *15*, 1800−1803. (d) Parrick, J.; Yahya, A.; Ijaz, S.; Yizun, J. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2009−2015. (e) Hinman, R. L.; Bauman, C. P. *J. Am. Chem. Soc*. **1964**, *29*, 1206−1215. (f) Chien, C.-S.; Suzuki, T.; Kawasaki, T.; Sakamoto, M. *Chem. Pharm. Bull*. **1984**, *32*, 3945−3951. (g) Ohnuma, T.; Kasuya, H.; Kimura, Y.; Ban, Y. *Heterocycles* **1982**, *17*, 377−380. (h) Walser, A.; Blount, J. F.; Fryer, R. I. *J. Org. Chem*. **1973**, *38*, 3077−3084. (i) Acheson, R. M.; Prince, R. J.; Proctor, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 595−598. (j) Hino, T.; Torisawa, Y.; Nakagawa, M. *Chem. Pharm. Bull*. **1982**, *30*, 2349−2356.

10.1021/jo020543m CCC: $25.00
Published on Web 12/14/2002

TABLE 1. Preparation of Indolylmalonates



1a, b, d, e **2a, b, c, d, e**

compd	R	time (h)	yield (%)
a	H	24	82[b]
b	F	18	70
c[c]	OH	_[c]	_[c]
d	OMe	1	76
e	OBn	1	88

[a] Me_2CO_3, 2.2 equiv of NaH, rt. [b] Prepared according to the published procedure.[10] [c] Compound **2c** was obtained by demethylation of **2d** with BBr_3 in 53% yield.

have engaged in the exploration of new synthetic routes for the formation of 2-hydroxyindolenines. Accordingly, we are interested in the synthetic utilization of 3-indolylmalonates as substrates, since they are expected to show various competitive reactivities attributable to both the benzene and the heterocyclic ring, when reacted with bromine. Thus, in indoles, a strong deactivating substituent at the pyrrole ring or a strong activating substituent at the benzene ring has been recognized to increase the regiospecificity of the later to electrophilic substitution.[9]

In this work, we have investigated the effects of both the electronic and the steric effects on the reaction of 5-substituted 1-carbomethoxy-3-indolylmalonates (**2a**−**e**) with bromine in order to rationalize its mechanism and to further demonstrate their synthetic availability as building blocks toward complicated naturally occurring and modified indole derivatives.

Results

5-Substituted 1-carbomethoxyl-3-indolylmalonates **2a**,**b**,**d**,**e** were prepared from the corresponding methyl 3-indolyl acetates **1a**,**b**,**d**,**e** by Claisen condensation with dimethyl carbonate in the presence of sodium hydride in good yields (70−88%) as shown in Table 1. The starting materials **1** were previously synthesized by hydrolysis and esterification of the corresponding 3-indoleacetonitrile.[10] The demethylation of **2d** was performed with BBr_3 to furnish the desired product **2c** in moderate yield (see Table 1).

When indolylmalonates **2a**−**e** were stirred with 2 equiv of Br_2 in both CCl_4 and AcOH at room temperature, aromatic bromination and oxidation were found to be competing processes which afforded mixtures with variable composition of bromoindolylmalonates (**3**−**8**), indolylidenemalonates (**9**−**12**), and bromoindolylidenemalonates (**13**−**18**). The reactants and the products from our study are summarized in Scheme 1. The percentages of products and the reaction conditions are presented in Table 2.

Fluorine Substituent. Depending on the 5-substituent, either aromatic bromination becomes prominent or the oxidation occurs to give 2-hydroxy-3-indolylidenemalonates predominantly. Reaction of the parent (C5-H) indolylmalonate **2a** and the 5-fluorine derivative **2b**, with 2 equiv of Br_2 in the nonpolar solvent CCl_4 for 2 h, exhibited complete regioselectivity to give the corresponding 2-hydroxy-3-indolylidenemalonates **9** and **11** in 80 and 16% yield, respectively (entries 1 and 2). In the latter case, the presence of fluorine as electron-withdrawing substituent retards the oxidation reaction, and unreacted 5-fluoroindolylmalonate **2b** was recovered in 68%. However, when in another experiment **2b** was reacted with 2 equiv of Br_2 for 12 h, the yield of **11** increased to 66% (entry 3). Bromination of **2a** in the polar solvent AcOH for 2 h leads, in addition to the oxidized products 2-hydroxy- and 2-oxo-3-indolylidenemalonates **9** (44%) and **10** (20%), to a mixture of 2-bromo- and 2,6-dibromo-3-indolylmalonates **3** and **4** in a ca. 1:1 ratio, as determined by ^{1}H NMR spectral integration, in 18% global yield (entry 4). The same R_f value for **3** and **4** precluded isolation of **4**. Under the above conditions, the 5-fluorine derivative **2b** was transformed only into the oxidized products 5-fluoro-2-hydroxy- **11** (31%) and 5-fluoro-2-oxo-3-indolylidenemalonates **12** (46%) (entry 6). In a subsequent reaction with 1 equiv of Br_2, **11** was transformed into the oxoindolylidenemalonate **12** in 53% yield (entry 7).

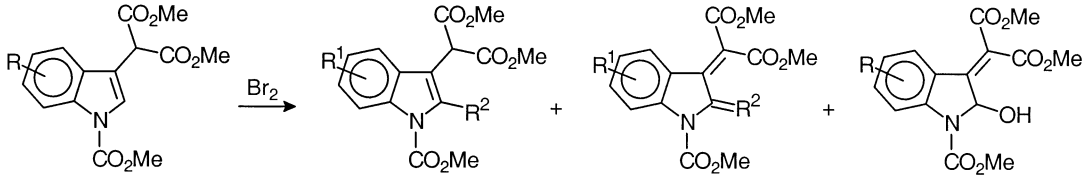
Oxygenated Activating Substituents. In the presence of ring-A oxygenated activating groups, ring bromination should be facilitated over the oxidation. Reaction of **2c**, with 1 equiv of Br_2 in CCl_4 for 2 h, revealed that ortho monobromination at C(4) was the favored initial reaction, leading to 4-bromo-5-hydroxy-3-indolylmalonate **5** in 58% yield, together with some 4,6-dibromo-5-hydroxy-3-indolylmalonate **6** (6%) and traces of 4-bromo-5-hydroxy 3-indolylidenemalonate **13** (entry 8). Compound **13**, of easy decomposition, could be characterized only by ^{1}H NMR and EIMS data. When, in another experiment, **2c** was reacted with 2 equiv of Br_2 in CCl_4 for 2 h the yield of **6** (21%) increased at the expense of **5** (45%) (entry 9). Finally, **6** was obtained as the major product (49%) upon reaction with 2 equiv of Br_2 in CCl_4 for 5 h. Small amounts of the 4-brominated regioisomer **5** (13%) were also observed (entry 10). In AcOH as solvent, the global yields of brominated products **5** and **6** in entries 11 and 12 were almost the same (57 and 56%, respectively), but the ratio of **5** to **6** decreased in time. These facts indicate that the 4,6-dibromoindolylmalonate **6** was formed by further bromination of the corresponding 4-bromoindole **5**. Compound **6** was further reacted with 1 equiv of Br_2 in AcOH for 0.5 h to afford the 4,6-dibromated 2-hydroxyindolylidenemalonate **18** in 30% yield (entry 13). By increasing the reaction time to 2 h, the yield of **18** decreases to 17%. The 4-bromo- and 4,6-dibromoindolylmalonates **5** and **6** were isolated and then identified by ^{1}H NMR and mass spectroscopy.

(8) (a) Bourlot, A. S.; Desarbre, E.; Mérour, J. Y. *Synthesis*, **1994**, 411−416. (b) Güler, R.; Borschberg, H.-J. *Tetrahedron Lett*. **1994**, *35*(6), 865−868. (c) Peterson, A. C.; Cook, J. M. *J. Org. Chem*. **1995**, *60*, 120−129.

(9) Brennan, M. R.; Erickson, K. L.; Szmalc, F. S.; Tansey, M. J.; Thornton, J. M. *Heterocycles* **1986**, *24*, 2879−2885.

(10) Rozhkov, V. S.; Smushkevich, Y. I.; Suvorov, N. N. *Khim. Geterotsikl. Soedin*. **1980**, 55−58; *Chem. Abstr*. **1980**, *93*, 8124j.

SCHEME 1. Reaction of Indolylmalones with Bromine



2a: R = H

3: R^1 = H, R^2 = Br
4: R^1 = 6-Br, R^2 = Br

9: R^1 = H, R^2 = H, OH
10: R^1 = H, R^2 = O

2b: R = F

11: R^1 = 5-F, R^2 = H, OH
12: R^1 = 5-F, R^2 = O

2c: R = OH

5: R^1 = 4-Br, 5-OH, R^2 = H
6: R^1 = 4,6-diBr, 5-OH, R^2 = H

13: R = 4-Br, 5-OH

2d: R = OMe

7: R^1 = 4-Br, 5-OMe, R^2 = H

14: R = 4-Br, 5-OMe
15: R = 6-Br, 5-OMe

2e: R = OBn

5: R^1 = 4-Br, 5-OH, R^2 = H
8: R^1 = 4-Br, 5-OBn, R^2 = H

16: R = 4-Br, 5-OBn
17: R = 6-Br, 5-OBn

6: R = 4,6-diBr, 5-OH

18: R = 4,6-diBr, 5-OH

TABLE 2. Products and Yields (%)[a] in the Reaction of Indolylmalonates 2 and 6 and Indolylidenemalonate 11 with Bromine[b]

entry	solvent		equiv of Br_2	time (h)	ring bromination[c–f]	oxidation	ring bromination[e–g] and oxidation
	CCl_4	AcOH					
1	**2a**		2	2		**9** (80)	
2	**2b**[h]		2	2		**11** (16)	
3	**2b**		2	12		**11** (66)	
4		**2a**	2	2	**3** (9)[c] + **4** (9)[d]	**9** (44) + **10** (20)	
5		**2a**[i]	1	2	**3** (11)[c]	**9** (70) + **10** (2)	
6		**2b**	2	5		**11** (31) + **12** (46)	
7		**11**	1	5		**12** (53)	
8	**2c**		1	2	**5** (58)[e] + **6** (6)[f]		**13** (traces)[e]
9	**2c**		2	2	**5** (45)[e] + **6** (21)[f]		**13** (traces)[e]
10	**2c**		2	5	**5** (13)[e] + **6** (49)[f]		**13** (traces)[e]
11		**2c**	2	2	**5** (27)[e] + **6** (30)[f]		**13** (9)[e]
12		**2c**	2	5	**5** (14)[e] + **6** (42)[f]		**13** (7)[e]
13		**6**	1	0.5			**18** (30)[f]
14	**2d**		2	3	**7** (46)[d]		**14** (27)[e] + **15** (25)[g]
15		**2d**	2	5	**7** (70)[d]		**15** (25)[g]
16		**2d**	3	6	-		**14** (52)[e] + **15** (27)[g]
17	**2e**		2	2	**5** (57)[d] + **8** (26)[d]		
18		**2e**	2	5	**8** (56)[d]		**16** (17)[e] + **17** (23)[g]

[a] Percentages of isolated reaction products. [b] Reactions carried out at room temperature. [c] Ring bromination at C(2). [d] Ring bromination at C(2,6). [e] Ring bromination at C(4). [f] Ring bromination at C(4,6). [g] Ring bromination at C(6). [h] Unreacted starting material was recovered in 68% yield. [i] Unreacted starting material was recovered in 10% yield.

In an extension of this investigation, we studied the unsymmetrical methoxyl and benzyloxyl substituents. When 5-methoxyindolylmalonate **2d** was stirred with 2 equiv of Br_2 in CCl_4 for 3 h, electrophilic attack at the C(4) position afforded the 4-bromoindole **7** (46%) as the major product. An interesting observation is that, in this case, besides the expected 4-bromo-2-hydroxy-3-indolylidenemalonate **14** (27%), the 6-brominated regioisomer **15** (25%) was also formed (entry 14). On the other hand, treatment of **2d** with 2 equiv of Br_2 in AcOH for 5 h afforded **7** (70%) and only the regioisomer **15** (25%) (entry 15). One noticeable feature of this conversion is that when the reaction time is extended from 2 to 5 h in the presence of 3 equiv of Br_2 (entry 16), the 4- and 6-brominated indolylidenemalonates **14** (52%) and **15** (27%) were formed as the sole products. In all sets of conditions, not even traces of 6-brominated indole were found.

When 5-benzyloxyindole **2e** was subjected to bromination in CCl_4 for 2 h, the 5-benzyloxy-4-bromo-3-indolylmalonate **8** was isolated in only 26% yield. In addition, unexpected debenzylated 4-bromo-5-hydroxyindole derivative **5** (57%) was also obtained (entry 17). Bromination of **2e** in AcOH for 5 h provided 4-bromoindole derivative **8** (56%) together with 4-bromo- and 6-bromo-3-indolylidenemalonates **16** (17%) and **17** (23%). Under these reaction conditions, not even traces of debenzylated derivative **5** were found (entry 18).

Discussion

Reactivity. At first, a number of reaction variables were investigated, e.g., solvent, molar ratio of bromine and reaction time. Although it is know that the use of polar solvents such as AcOH enhances the reactivity of bromine to electrophilic bromination,[11] except for **2a** and **2b**, the conversions of **2c**−**e** (Table 2) were slightly dependent on the solvent effect. For the compounds studied, the regiochemistry of the bromination was mainly dependent on the electronic effects and steric hindrance of the substituent in the benzene ring. The oxidation reaction at the pyrrole moiety of indolylmalonates **2a** and **2b** was not surprising since the N(1) protecting group deactivated the indole core and permitted the oxidation as the principal pathway.[6] This reaction is slowed with the electron-withdrawing 5-fluorine substituent.

In the case of **2c**−**e**, two contrasting factors were involved in the electrophilic vs oxidation process. The presence of an electron-withdrawing group at the N(1) position deactivates the indole nucleus to electrophilic attack. However, the oxygenated activating groups (OH, OMe, OBn) are expected to promote the electrophilic bromination on the benzene moiety. As can be seen in Table 2, the hydroxyl group in **2c** activates the aromatic ring for electrophilic bromination at the ortho positions with high chemospecificity, only a small amount of a brominated-oxidized product was detected. The bromination initially took place at the C(4) position to give regioselectively, by precise optimization of reaction conditions, the 4-bromoindole derivative **5**. Further bromination at the C(6) position can be easily effected by increasing the molar ratio of bromine and the reaction time.

With 5-methoxyindolylmalonate **2d**, a remarkable feature becomes apparent: although electronically, the methoxyl group is expected to influence the product formation in a similar way than the hydroxyl group in **2c**, the reactivity of **2d** shows a markedly difference. In **2d**, ring bromination and oxidation occur under the standard conditions (entries 14 and 15), monobrominated products at C(4) **7** and **14** and at C(6) **15** were obtained in ca. 3:1 ratio. In addition, the steric effect of the methoxyl group is important enough to prevent the formation of 4,6-dibrominated products despite an excess of molar ratio of bromine (entry 16). Under these conditions, the presence of a methoxyl group promotes oxidation of the indole double bond rather than a second ring bromination, so that ring dibromination is completely overruled in **2d**. Likewise, the reaction of 5-benzyloxyindolylmalonate **2e**, only gave the monobrominated products.

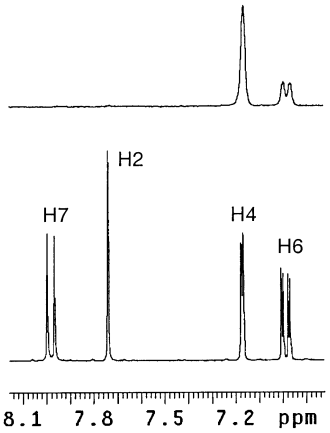


FIGURE 1. Positive NOEs of different magnitude which occur at H4 and H6 upon irradiation of the 5-methoxyl group of **2d**.

The different reactivity with which the C(4) and C(6) positions in **2d** and **2e** undergo electrophilic bromination is a consequence of two factors: the unequal π-electron density at the positions ortho to methoxyl or benzyloxyl substituents, and the steric interactions developed upon electrophilic attack between the alkoxyl group and the approaching bromine. The conformational preference of the unsymmetrical oxygenated groups,[12] derived from NMR studies, ab initio quantum chemistry (HF/3-21G*) and X-ray diffraction analysis, are all interpreted as consistent with a conformer in which the 5-O-alkyl group lies predominantly s-cis to H4. Thus, in DMSO-d_6 positive NOEs of different magnitude occur at the H4 (18%) and H6 (8%) signals upon irradiation of the 5-methoxyl group of **2d** (Figure 1). Ab initio calculations of the conformer stabilities for **2d** and **2e** predict the s-cis to H4 form to be 1.38 and 1.28 kcal/mol, respectively, lower in energy than the s-trans form, corresponding to 91% and 90% abundance of the s-cis to H4 form, respectively, at 298 K. The X-ray crystal structure for **2e**[13] is shown in Figure 2. The C4−C5−O5−C15 torsion angle value of −5.3° is in agreement with the NMR results and theoretical predictions. The structures and conformation of the 4-bromo-5-methoxyindole derivative **7**,[14] and the 5-hydroxylated compounds **2c**[15] and **5**[16] were also determined by X-ray diffraction studies. In these cases the C4−C5−O5−C15 torsion angle value is 170.3° for **7**, whereas for

(11) (a) Kruse, L. I.; Meyer, M. D. *J. Org. Chem*. **1984**, *49*, 4761−4768. (b) Tani, M.; Ikegami, H.; Tashiro, M.; Hiura, T.; Tsukioka, H.; Kaneko, C.; Notoya, T.; Shimizu, M.; Uchida, M.; Aida, Y.; Yokoyama, Y.; Murakami, Y. *Heterocycles* **1992**, *34*, 2349−2362. (c) Somei, M.; Fukui, Y.; Hasegawa, M.; Oshikiri, N.; Hayashi, T. *Heterocycles* **2000**, *53*, 1725−1736.

(12) (a) Kruse, L. I.; DeBrosse, C. W.; Kruse, C. H. *J. Am. Chem. Soc*. **1985**, *107*, 5435−5442. (b) Ernst, L. *Angew. Chem*. **1976**, *15*, 303−304. (c) Joseph-Nathan, P.; García-Martínez, C.; Morales-Ríos, M. S. *Magn. Reson. Chem*. **1990**, *28*, 311−314.

(13) Colorless crystals of **2e** ($C_{22}H_{21}O_7N$) were grown from EtOAc/hexane. Data collection was conducted at 293 K on a triclinic crystal: *P*1(bar); a = 9.8474(5) Å, b = 10.3596(5) Å, c = 11.3164(5) Å, α = 78.055(1)°, β = 86.923(1)°, γ = 65.457(1)°; V = 1026.72(9) Å^3, Z = 2; R_1 = 4.5%, wR_2 = 11.9%, GOF = 1.038. CCDC[20] deposition no. 194861.

(14) Colorless crystals of **7** ($C_{16}H_{16}O_7NBr$) were grown from EtOAc/hexane. Data collection was conducted at 293 K on a monoclinic crystal: *C*2; a = 12.111(2) Å, b = 7.048(1) Å, c = 20.932(3) Å, β = 102.899(3)°; V = 1742.6(5) Å^3, Z = 4; R_1 = 5.7%, wR_2 = 15.6%, GOF = 1.073. CCDC[20] deposition no. 194863.

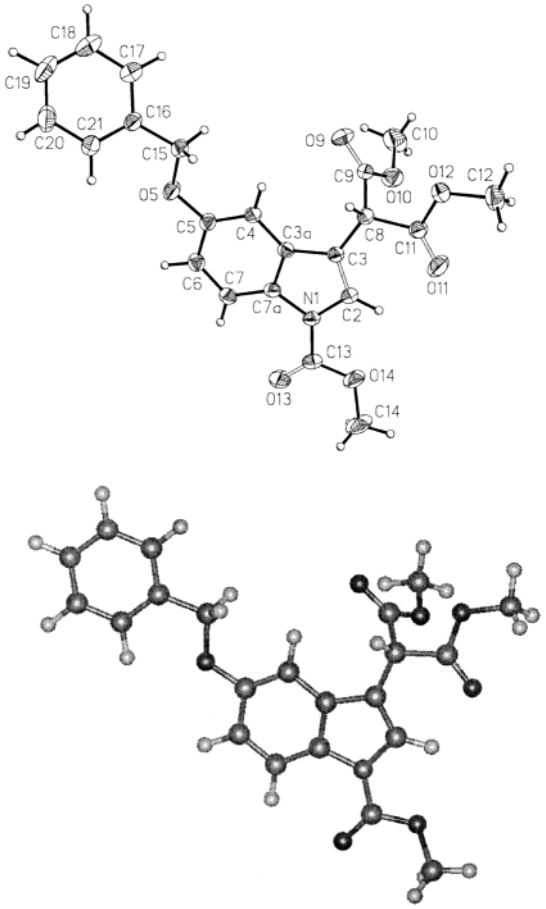


FIGURE 2. X-ray diffraction (top) and ab initio computed structure (bottom) of **2e**.

2c and **5** the C4−C5−O5−H5 torsion angle values are −11.4° and −165.8°, respectively (see the Supporting Information).

Mechanistic studies. A reasonable mechanism for the formation of 2-hydroxyindolenines from 3-indolylmalonates is outlined in Scheme 2. The first step in this proposal involves an electrophilic addition of Br_2 to the C(2)═C(3) double bond to form perhaps a bromonium ion intermediate **19**, followed by H8-abstraction generating the labile intermediate 2-bromoindolenine **20**, which is further hydrolyzed during the aqueous workup procedure to afford the corresponding 2-hydroxyindolenines **9**, **11**, and **13**−**18**. To test this hypothesis, the conversion of **2a** was followed by EI mass spectrometry. Spectra were taken immediately after the addition of Br_2 (2 equiv) to a solution of **2a** in CCl_4 and from then on every 30 min. The new diagnostic peaks, M^+ and $(M + 2)^+$ at 383 and 385 amu, respectively, which grew in during the course of the reaction, agree very well with those of the expected brominated indolenine **20** (Figure 3). No other products

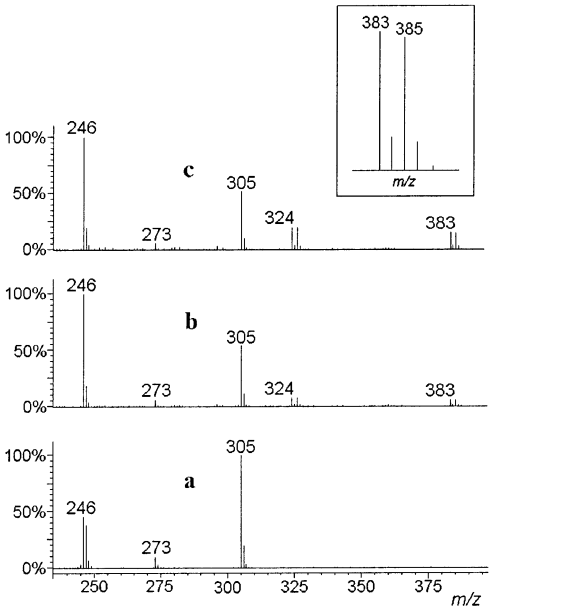
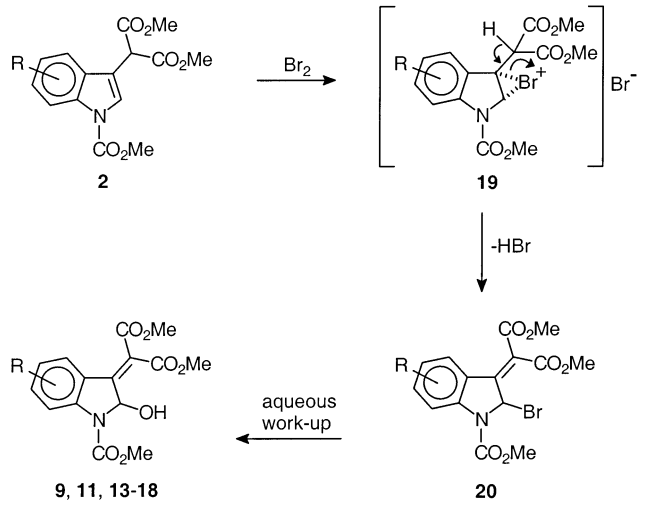


FIGURE 3. EIMS monitoring of the reaction of **2a** with Br_2 in CCl_4 at (a) $t = 0$, (b) $t = 1$ h, and (c) $t = 2$ h.

SCHEME 2



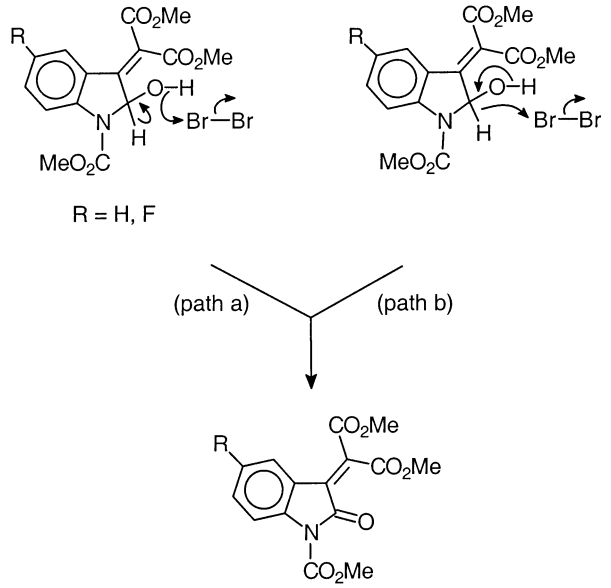
were identifiable until 2 h. Analysis by TLC (silica gel, 3:7 EtOAc/hexane) of this crude mixture revealed that **2a** was consumed and that **9** (R_f 0.15) is present together with a higher R_f value (0.47) intermediate **20** (estimated 75%) which transforms, on standing for several hours on the silica gel coated aluminum sheet, to **9**. In addition, when **2d** was reacted with Br_2 (2 equiv) at room temperature in CCl_4, MS monitoring of the reaction showed that two bromine atoms were consecutively incorporated into **2d**. The intermediate monobrominated product gradually disappeared from the reaction mixture, and the sole product containing two bromine atoms (according to MS data) was observed. These results provide strong support for a scenario where the oxidation reactions with Br_2 proceed via a 2-bromoindolenine and subsequent hydrolysis.

On the other hand, analysis of substituent effects on the product compositions (Table 2) revealed that a further oxidation of 2-hydroxy-3-indolylidenemalonates to 2-oxo derivatives is suppressed when increasing the electron-

(15) Colorless crystals of **2c** ($C_{15}H_{15}O_7N$) were grown from EtOAc/hexane. Data collection was conducted at 293 K on a triclinic crystal: *P*1(bar); $a = 7.9296(9)$ Å, $b = 8.5864(9)$ Å, $c = 11.618(1)$ Å, $\alpha = 81.308(2)°$, $\beta = 78.344(3)°$, $\gamma = 77.467(3)°$; $V = 751.5(1)$ Å^3, $Z = 2$; $R_1 = 7.1\%$, $wR_2 = 17.1\%$, GOF = 0.922. CCDC[20] deposition no. 194860.

(16) Colorless crystals of **5** ($C_{15}H_{14}O_7NBr$) were grown from EtOAc/hexane. Data collection was conducted at 293 K on a triclinic crystal: *P*1(bar); $a = 7.916(5)$ Å, $b = 9.289(5)$ Å, $c = 12.133(5)$ Å, $\alpha = 76.908(5)°$, $\beta = 72.999(5)°$, $\gamma = 85.391(5)°$; $V = 830.9(8)$ Å^3, $Z = 2$; $R_1 = 7.2\%$, $wR_2 = 16.6\%$, GOF = 0.987. CCDC[20] deposition no. 194862.

SCHEME 3



donating character of the 5-substituent. On this basis, the formation of 2-oxo-3-indolylidenemalonates **10** and **12** by oxidation of **9** and **11**, respectively, with bromine in the polar AcOH solvent is assumed to occur by removal of the hemiaminalic proton form C(2) and hydride transfer from oxygen (path a), rather than by hydride transfer from C(2) and proton removal from oxygen[17] (path b), as described in Scheme 3. In CCl_4, the oxidation did not proceed at all. A reaction mechanism involving the initial tautomerization of the exocyclic 3(8)-double bond to the 2,3-endocyclic position is ruled out, since tretment of **11** with catalytic amounts of H_2SO_4 in AcOD-d_3 for 10 h did not induced any change in its ^{1}H NMR spectrum.

In summary, a novel straightforward strategy for highly functionalized 2-hydroxyindolenines was developed based on indolylmalonates that employs very mild reaction conditions. This methodology permits entry into versatile indole building blocks for the syntheses of indole alkaloids and nonnatural analogues.

Experimental Section

General Methods. Melting points are uncorrected. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography was performed using silica gel 60 (230−400 mesh). IR spectra were obtained using a FT spectrophotometer. NMR spectra were recorded on spectrometers operating at 300 and 75 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts are reported in ppm downfield from tetramethylsilane. NOE enhancements were determined from 1D difference NOE ^{1}H NMR spectra obtained by subtraction of two spectra acquired at identical conditions except for irradiation frequency. LREIMS and HRMS were measured using direct inlet spectrometers. All the commercial grade reagents were used without further purification. Calculations for the ab initio HF/3-21G*-optimized structures were performed using PC-based programs.[18]

General Procedure for the Preparation of Indolyl Acetates 1b,d,e. Compounds **1b**, **1d**, and **1e** were prepared in a manner similar to that previously described for **1a**.[10] A mixture of 7.8 mmol of the appropriate acetonitrylindole[19] in 20 mL of aqueous 20% KOH was refluxed for 5 h, and after cooling, the reaction was made acid with 10 N aqueous HCl. The resulting suspension was vacuum filtered, and the precipitate was washed with water. The residue was purified by crystallization (EtOAc). All indolylacetic acids were characterized by NMR affording spectral data in agreement with their structure.

A solution of the corresponding indolylacetic acid in anhydrous MeOH (25 mL) was stirred with 10 N HCl (0.1 mL) at reflux for 2 h. The mixture was purified by flash column chromatography on silica gel (EtOAc/hexane, 1:4) or Kugelrohr distillation (110−122 °C, 0.5 mmHg) to afford a solid in overall yields of 63−66%.

Methyl (5-fluoro-1*H*-indole-3-yl)acetate (1b): slightly pink solid; mp 71−73 °C on standing; R_f 0.20 (EtOAc/hexane 1:4); IR ($CHCl_3$) ν_{max} 3042, 1734, 1488, 1176 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.05 (1H, br s, NH), 7.34 (1H, dd, J = 9.0, 4.7 Hz, H7), 7.32 (1H, br s, H2), 7.22 (1H, dd, J = 10.1, 2.5 Hz, H4), 6.91 (1H, td, J = 9.0, 2.5 Hz, H6), 3.72 (2H, s, H8), 3.60 (3H, s, CO_2Me); ^{13}C NMR (DMSO-d_6) δ 171.9 (C=O), 156.8 (d, J = 231.2 Hz, C5), 132.8 (C7a), 127.4 (d, J = 10.1 Hz, C3a), 126.2 (C2), 112.4 (d, J = 9.8 Hz, C7), 109.2 (d, J = 25.9 Hz, C6), 107.3 (d, J = 4.9 Hz, C3), 103.2 (d, J = 23.3 Hz, C4), 51.5 (OMe), 30.4 (C8); EIMS m/z 207 (M^+, 35), 148 (100), 101 (11); HRMS (FAB) m/z 207.0703 (M^+, $C_{11}H_{10}NO_2F$ requires 207.0696).

Methyl (5-methoxy-1*H*-indole-3-yl)acetate (1d): slightly yellow solid; mp 70−71 °C on standing; R_f 0.20 (EtOAc/hexane 1:4); IR ($CHCl_3$) ν_{max} 3012, 1732, 1220, 1058 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.79 (1H, br s, NH), 7.26 (1H, d, J = 8.8 Hz, H7), 7.21 (1H, d, J = 2.3 Hz, H2), 6.99 (1H, d, J = 2.4 Hz, H4), 6.75 (1H, dd, J = 8.8, 2.4 Hz, H6), 3.75 (3H, s, OMe), 3.72 (2H, s, H8), 3.61 (3H, s, CO_2Me); ^{13}C NMR (DMSO-d_6) δ 172.0 (C=O), 153.1 (C5), 131.2 (C7a), 127.4 (C3a), 124.6 (C2), 112.0 (C7), 111.1 (C6), 106.7 (C3), 100.3 (C4), 55.3 (OMe), 51.4 (OMe ester), 30.6 (C8); EIMS m/z 219 (M^+, 72), 160 (100), 145 (18); HRMS (FAB) m/z 219.0895 (M^+, $C_{12}H_{13}NO_3$ requires 219.0895).

Methyl (5-benzyloxy-1*H*-indole-3-yl)acetate (1e): slightly pink solid; mp 41−43 °C on standing; R_f 0.20 (EtOAc/hexane 1:4); IR ($CHCl_3$) ν_{max} 3070, 1712, 1626, 1248 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 10.79 (1H, br s, NH), 7.47−7.30 (5H, m, Ar), 7.24 (1H, d, J = 8.8 Hz, H7), 7.19 (1H, d, J = 2.4 Hz, H2), 7.07 (1H, d, J = 2.4 Hz, H4), 6.80 (1H, dd, J = 8.8, 2.4 Hz, H6), 5.06 (2H, s, OCH_2), 3.69 (2H, d, J = 0.6 Hz, H8), 3.57 (3H, s, OMe); ^{13}C NMR (DMSO-d_6) δ 172.0 (C=O), 152.2 (C5), 137.8 (C_i), 131.4 (C7a), 128.3 (C_m), 127.6 (C_o), 127.4 (C_p, C3a), 124.8 (C2), 112.1 (C7), 111.8 (C6), 106.7 (C3), 102.0 (C4), 69.8 (OCH_2), 51.5 (OMe), 30.6 (C8); EIMS m/z 295 (M^+, 84), 204 (100), 146 (56), 91 (43); HRMS (FAB) m/z 295.1213 (M^+, $C_{18}H_{17}NO_3$ requires 295.1208).

General Procedure for the Preparation of Malonates 2. Compounds **2b**, **2d**, and **2e** were prepared in a manner similar to that previously described for **2a**.[10] To a solution of the appropriate methyl 3-indolyl acetate **1** (4.4 mmol) in Me_2CO_3 (30 mL) under argon at rt was added NaH (0.27 g, 11.1 mmol). The mixture was stirred at rt until TLC analysis showed complete loss of starting material 18 h for **2b**, 1 h for **2d**, and 16 h for **2e**. After brine (60 mL) was added to the reaction mixture, the organic layer was separated, dried over Na_2SO_4, and evaporated. The resultant crude product was purified by flash chromatography on silica gel.

(17) Swain, C. G.; Wiles, R. A.; Bader, R. F. W. *J. Am. Chem. Soc.* **1961**, *83*, 1945−1950.

(18) Hehre, W. J.; Deppmeier, B. J.; Klunzinger, P. E. *A PC Spartan Pro Tutorial*; Wavefunction, Inc.: Irvine, CA, 1999.

(19) (a) Stoll, A.; Troxler, F.; Peyer, J.; Hofmann, A. *Helv. Chim. Acta* **1955**, *38*, 1452−1472. (b) US 4283410.

(20) The authors have deposited atomic coordinates for the structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Crystallographic Data Center 12 Union Road, Cambridge CB2 1Z, U.K.

Dimethyl 2-(1-Carbomethoxy-1*H*-indol-3-yl)malonate (2a). Prepared from **1a** as colorless crystals (1.07 g, 81%): mp 109−111 °C (EtOAc/hexane) [lit.[10] 108−110 °C (MeOH)]; R_f 0.40 (EtOAc/hexane 3:7); IR ($CHCl_3$) ν_{max} 3026, 1741, 1448 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.12 (1H, d, J = 8.2 Hz, H7), 7.81 (1H, s, H2), 7.64 (1H, dd, J = 7.8, 1.2 Hz, H4), 7.38 (1H, td, J = 7.8, 1.2 Hz, H6), 5.36 (1H, s, H8), 4.00 (3H, s NCO_2Me), 3.71 (6H, s, 2 CO_2Me);^{13}C NMR (DMSO-d_6) δ 168.0 (2 CO_2Me), 150.6 (NCO_2Me), 134.6 (C7a), 128.7 (C3a), 125.1 (C2), 124.8 (C6), 123.0 (C5), 114.6 (C7), 113.1 (C3), 120.1 (C4), 54.2 (NCO_2Me), 52.4 (2 CO_2Me), 48.2 (C8); EIMS m/z 305 (M^+, 61), 246 (100), 174 (15); HRMS (FAB) m/z 305.0894 (M^+, $C_{15}H_{15}NO_6$ requires 305.0899).

Dimethyl 2-(1-Carbomethoxy-5-fluoro-1*H*-indol-3-yl)-malonate (2b). Prepared from **1b** as yellow solid (1.0 g, 70%): mp 71−73 °C (CH_2Cl_2/hexane); R_f 0.32 (EtOAc/hexane 1:4); IR ($CHCl_3$) ν_{max} 3020, 1738, 1266, 1196 cm^{-1}; ^1H NMR (DMSO-d_6) δ 8.11 (1H, dd, J = 9.4, 4.7 Hz, H7), 7.87 (1H, s, H2), 7.45 (1H, dd, J = 9.4, 2.6 Hz, H4), 7.24 (1H, td, J = 9.4, 2.6 Hz, H6), 5.39 (1H, s, H8), 4.00 (3H, s NCO_2Me), 3.79 (6H, s, 2 CO_2Me);^{13}C NMR (DMSO-d_6) δ 167.9 (2 CO_2Me), 158.5 (d, J = 237.3 Hz, C5), 150.4 (NCO_2Me), 131.2 (C7a), 129.9 (d, J = 10.3 Hz, C3a), 127.0 (d, J = 8.6 Hz, C2), 116.0 (d, J = 9.4 Hz, C7), 112.9 (d, J = 4.3 Hz, C3), 112.6 (d, J = 25.5 Hz, C6), 105.9 (d, J = 24.6 Hz, C4), 54.4 (NCO_2Me), 52.9 (2 CO_2Me), 48.2 (C8); EIMS m/z 323 (M^+, 47), 264 (100), 192 (17); HRMS (FAB) m/z 323.0791 (M^+, $C_{15}H_{14}NO_6F$ requires 323.0805).

Dimethyl 2-(1-Carbomethoxy-5-methoxy-1*H*-indol-3-yl)malonate (2d). Prepared from **1d** as colorless crystals (1.1 g, 76%): mp 145−146 °C (EtOAc); R_f 0.24 (EtOAc/hexane 1:4); IR ($CHCl_3$) ν_{max} 3014, 2838, 1738, 1264 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.98 (1H, d, J = 9.0 Hz, H7), 7.75 (1H, s, H2), 7.18 (1H, d, J = 2.6 Hz, H4), 6.99 (1H, dd, J = 9.0, 2.6 Hz, H6), 5.35 (1H, s, H8), 3.98 (3H, s NCO_2Me), 3.79 (3H, s, OMe), 3.72 (6H, s, 2 CO_2Me); ^{13}C NMR (DMSO-d_6) δ 168.0 (2 CO_2Me), 155.6 (C5), 150.5 (NCO_2Me), 129.8 (C3a), 129.1 (C7a), 125.5 (C2), 115.3 (C7), 113.3 (C6), 113.0 (C3), 102.9 (C4), 55.4 (OMe), 54.1 (NCO_2Me), 52.7 (2 CO_2Me), 48.2 (C8); EIMS m/z 335 (M^+, 68), 276 (100), 217 (6); HRMS (FAB) m/z 335.1021 (M^+, $C_{16}H_{17}NO_7$ requires 335.1005).

Dimethyl 2-(5-Benzyloxy-1-carbomethoxy-1*H*-indol-3-yl)malonate (2e). Prepared from **1e** as yellow crystals (1.6 g, 88%): mp 109−110 °C (Et_2O); R_f 0.24 (EtOAc/hexane 1:4); IR ($CHCl_3$) ν_{max} 3016, 1738, 1264, 1022 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.98 (1H, d, J = 9.1 Hz, H7), 7.73 (1H, s, H2), 7.48−7.32 (5H, m, Ar), 7.27 (1H, d, J = 2.4 Hz, H4), 7.06 (1H, dd, J = 9.1, 2.4 Hz, H6), 5.32 (1H, s, H8), 5.11 (2H, br s, OCH_2), 3.96 (3H, s, NCO_2Me), 3.68 (6H, s, 2 CO_2Me); ^{13}C NMR (DMSO-d_6) δ 168.1 (2 CO_2Me), 154.7 (C5), 150.6 (NCO_2Me), 137.1 (C_i), 129.8 (C3a), 129.3 (C7a), 128.4 (C_m), 127.8 (C_p), 127.7 (C_o), 125.7 (C2), 115.4 (C7), 114.0 (C6), 113.0 (C3), 104.3 (C4), 69.7 (OCH_2), 54.2 (NCO_2Me), 52.8 (2 CO_2Me), 48.2 (C8); EIMS m/z 411 (M^+, 95), 320 (100), 91 (50); HRMS (FAB) m/z 411.1304 (M^+, $C_{22}H_{21}NO_7$ requires 411.1318).

Dimethyl 2-(1-Carbomethoxy-5-hydroxy-1*H*-indol-3-yl)-malonate (2c). To a solution of malonate **2d** (0.21 g, 0.6 mmol) in $CHCl_3$ (13 mL) under argon at 0 °C was added BBr_3 (2.1 mL of a 1 M solution in CH_2Cl_2). The reaction mixture was stirred for 2.5 h at this temperature and quenched by adding water (5 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 30 mL), and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and evaporated. The resultant crude product was purified by flash chromatography on silica gel (EtOAc/hexane 4:1) to give **2c** as colorless crystals (0.1 g, 53%): mp 172−173 °C (EtOAc/hexane); R_f 0.08 (EtOAc/hexane 1:4); IR ($CHCl_3$) ν_{max} 3510, 3020, 1740, 1226 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.32 (1H, s, OH), 7.89 (1H, d, J = 8.8 Hz, H7), 7.72 (1H, s, H2), 6.96 (1H, d, J = 2.3 Hz, H4), 6.84 (1H, dd, J = 8.8, 2.3 Hz, H6), 5.25 (1H, s, H8), 3.97 (3H, s NCO_2Me), 3.71 (6H, s, 2 CO_2Me); ^{13}C NMR (DMSO-d_6) δ 167.9 (CO_2Me), 153.4 (C5), 150.6 (NCO_2Me), 129.8 (C3a), 128.4 (C7a), 125.5 (C2), 115.2 (C7), 113.9 (C6), 112.8 (C3), 104.9 (C4), 54.0 (NCO_2Me), 52.7 (CO_2Me), 48.5 (C8); EIMS m/z 321 (M^+, 44), 262 (100), 190 (9); HRMS (FAB) m/z 321.0856 (M^+, $C_{15}H_{15}NO_7$ requires 321.0849).

General Procedure for Bromination of Malonates. To a solution of the appropriate malonate **2a**−**e** (0.64 mmol) in CCl_4 (45 mL) or AcOH (30 mL) was added Br_2 (1.28 mmol, 0.066 mL) at rt at once, and the resulting mixture was stirred at this temperature during the time indicated in Table 2. After water (15 mL) was added to the reaction mixture, the stirring was continued at rt for 20 min. The aqueous phase was extracted with $CHCl_3$ or EtOAc (2 × 80 mL), and the combined organic layers were washed with brine (3 × 40 mL), and evaporated. The residue was dissolved in aq 20% THF (70 mL) and refluxed for 2 h. THF was then removed under reduced pressure and the residue was extracted with EtOAc (2 × 50 mL), washed with brine, dried over Na_2SO_4, and evaporated to afford a yellow oil. Flash chromatography on silica gel (EtOAc/hexane) afforded the products indicated in Scheme 1. Individual reaction yields are given in Table 2.

Acknowledgment. This research was partially suported by CONACYT (Mexico). N.F.S.-S. gratefully acknowledges CONACYT for a doctoral fellowship. We thank I. Q. Luis Velasco Ibarra (Instituto de Química, UNAM) for recording the HRMS.

Supporting Information Available: X-ray structure data, ^1H and ^{13}C spectra, computational data, and characterization data for compounds **3**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO020543M