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Synthesis of caulersin and its isomers by reaction of indole-2,3-dicarboxylic anhydrides with methyl indoleacetates

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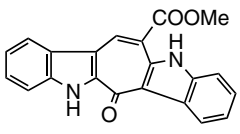
Abstract—1-Benzenesulfonylindole-2,3-dicarboxylic anhydride was reacted with methyl 1-benzenesulfonylindole-2-acetate to give the corresponding 2-acylindole-3-carboxylic acid as the sole product in high yield, which could be converted to caulersin in four steps. In a similar manner, three isomers A, B, and C were synthesized by reaction of indole-2,3-dicarboxylic anhydrides with methyl indoleacetates.

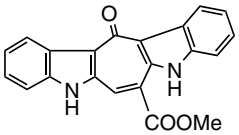
Staurosporine,[1] rebeccamycin,[2] and arcyriaflavins,[3] a family of bisindole natural products, have an extra six-membered cyclic ring between the two indole rings and show a variety of important biological activities. Caulersin[4] and caulerpin[5] are also members of bisindole alkaloid, which have an extra seven- and eight-membered cyclic ring between the two indole rings, which are incorporated directly with the carbonyl group. Caulersin, was isolated in 1997 from the alga *Caulerpa serrulata*,[4] but its biological activity was not reported. Caulersin was synthesized by Molina[6] and Bergman.[7] However, the structure of natural caulersin is not clear because Bergman reported that the structure of synthetic caulersin was confirmed by X-ray diffraction study, but ^{13}C NMR spectral data of natural caulersin[4] was not the same as that of natural caulersin. Three isomers A, B, and C, are thought by structural analysis of the structure of natural possible caulersin considering the binding pattern of one cycloheptatriene ring and two indole rings.

Recently, we showed that indole-2,3-dicarboxylic anhydrides **1** were useful synthons in the synthesis of natural products, murrayaquinone-A,[8] ellipticine,[9] and olivacine,[10] 2-acylindoles,[11] and cyclopent[3,4-*b*]indol-3-ones.[12] In this letter, we report the efficacy of the anhydrides **1** and its application to a simple and useful synthesis of caulersin and its isomer A, B, and C by reaction of **1** with methyl indoleacetates to confirm the structure of caulersin.

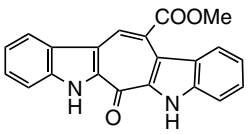
Reaction of 1-benzenesulfonylindole-2,3-dicarboxylic anhydride **1a** with methyl 1-benzenesulfonylindole-2-acetate **2** in dichloromethane in presence of titanium(IV) chloride to afford 2-acylindole-3-carboxylic acid **3** in quantitative yield. Treatment of the 3-carboxylic acid **3** with oxalyl chloride, followed by tetrabutyltin hydride in the presence of $Pd(PPh_3)_4$ (rt, in toluene) led to the aldehyde **4** in 77% yield. Cyclization of **4** to *N*,*N*′-dibenzenesulfonylcaulersin **5** was performed by NaH treatment in THF at rt in 67% yield. Debenzenesulfonylation of **5** with tetrabutylammonium fluoride[13] in THF gave caulersin[14] in 91% yield. We found that caulersin synthesized by us is the same as the compound synthesized by Bergman and not the same as natural caulersin by



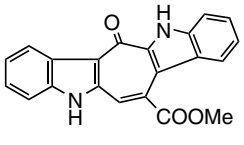
caulersin



isomer A



isomer B



isomer C

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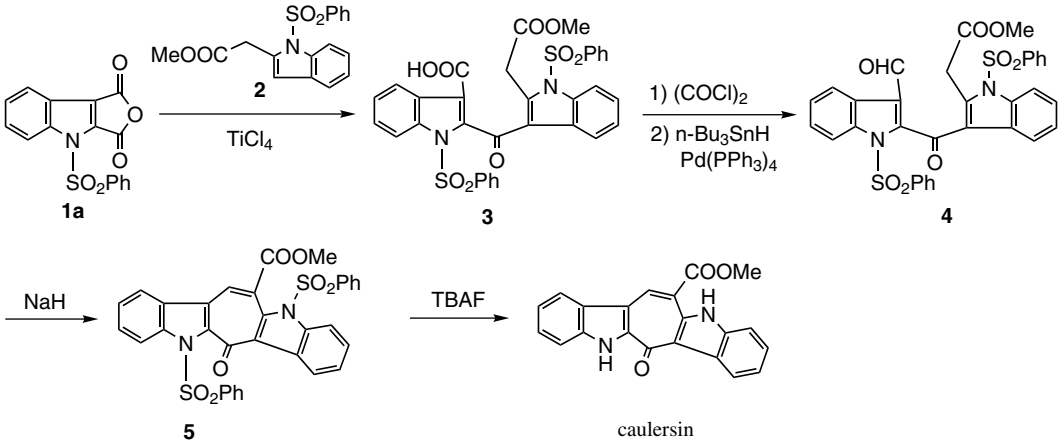
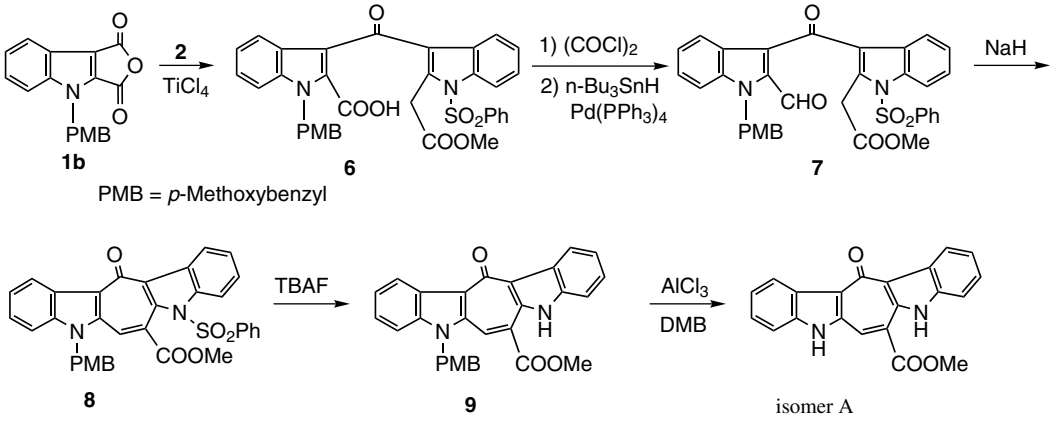
comparison the ^{1}H NMR and ^{13}C NMR spectral data among the three compounds (Scheme 1).

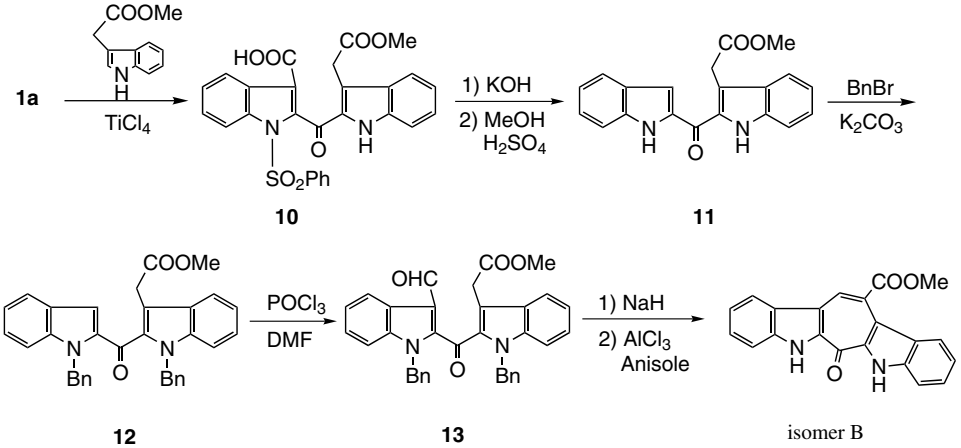
Next, we would like to synthesize isomer A because we encountered a Hayashi rearrangement in the synthesis of acid chloride.[15] 1-(*p*-Methoxybenzyl)indole-2,3-dicarboxylic anhydride **1b** was reacted with **2** in dichloromethane in the presence of titanium(IV) chloride to afford 3-acylindole-2-carboxylic acid **6** in 30% yield. Treatment of the carboxylic acid **6** with oxalyl chloride, followed by tetrabutyltin hydride in the presence of $Pd(PPh_3)_4$ (rt, in toluene) led to the aldehyde **7** in 58% yield. Cyclization of **7** to **8** was performed by treatment with NaH in THF at rt in 43% yield. Debenzenesulfonylation of **8** with tetrabutylammonium fluoride in THF gave **9** (77%), followed by treatment of **9** with aluminum(III) chloride in 1,3-dimethoxybenzene (DMB) to provide caulersin isomer A[16] in 70% yield. However, the ^{1}H NMR and ^{13}C NMR spectral of isomer A was not the same as those of natural caulersin (Scheme 2).



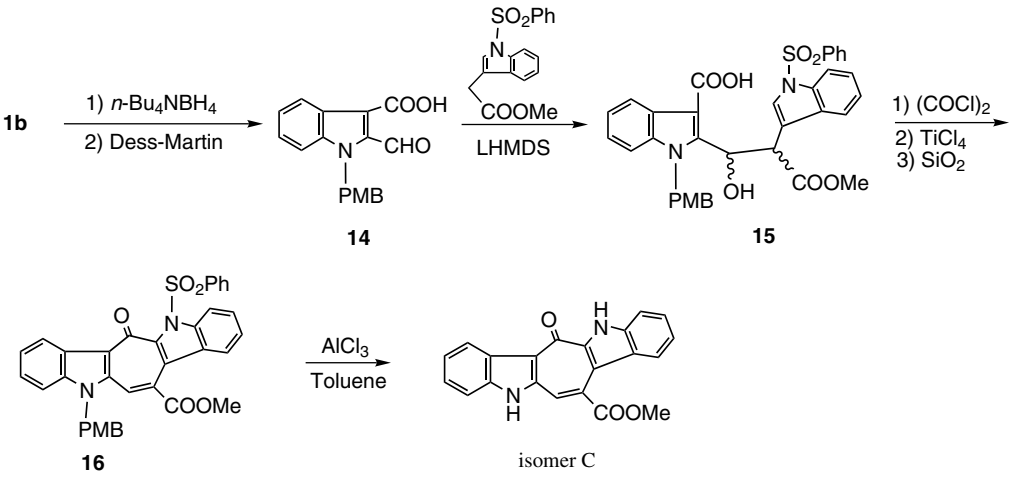
Scheme 1. Synthetic route to caulersin.



Scheme 2. Synthetic route to isomer A.



Scheme 3. Synthetic route to isomer B.



Scheme 4. Synthetic route to isomer C.

Isomers B and C were synthesized as follows. Reaction of the anhydride **1a** with methyl indole-3-acetate in dichloromethane in the presence of titanium(IV) chloride gave 3-acylindole-2-carboxylic acid **10** in 85% yield. Treatment of the carboxylic acid **10** with hot aqueous potassium hydroxide solution, followed by dry methanol in the presence of sulfuric acid led to the ketone **11** in 41% yield. Benzylation of **11** with benzyl bromide in the presence of potassium carbonate in hot acetonitrile afforded **12** (quant.), which was formylated by DMF and $POCl_3$ to provide the corresponding aldehyde **13** in 59% yield. Cyclization of **13** with NaH in THF gave a *N*,*N*′-dibenzyl derivative (64%), which was treated with tetrabutylammonium fluoride in THF to give isomer B[17] in 69% yield (Scheme 3).

Reduction of **1b** with tetra-*n*-butylammonium borohydride in THF (86%), followed by Dess–Martin oxidation gave 2-formylindole-3-carboxylic acid **14** in 97% yield. The aldehyde **14** was reacted with methyl 1-benzenesulfonylindole-3-acetate in the presence of lithium hexamethyl-disilazane (LHMDS) in THF to provide the β-hydroxy ester **15** (50%), which could be converted by treatment of oxalyl chloride, then titanium(IV) chloride and silica gel to afford the cyclization compound **16**[18] in 35% yield. Finally, deprotection of **16** with aluminum(III) chloride in toluene was performed to give isomer C[19] in 56% yield (Scheme 4).

We compared the ^{1}H NMR and ^{13}C NMR spectra of natural caulersin, synthetic caulersin, isomers A, B, and C. The spectra of natural caulersin are quite different from those of isomers A, B, and C, but are the same as that of synthetic caulersin except two peaks (δ 136.9 and 119.4) of the ^{13}C NMR spectra. However, we could show the real structure of caulersin is the proposed structure reported by Su[4] from the synthesis of caulersin and three isomers, A, B, and C by using indole-2,3-dicarboxylic anhydrides (Table 1).

Table 1. ^{1}H NMR and ^{13}C NMR spectral data of caulersin, isomers A, B, and C

Natural caulersin[4]	Synthetic caulersin	Isomer A	Isomer B	Isomer C
^{1}H NMR spectral data				
13.14 s	12.95 s	12.71 s	12.79 s	12.83 s
12.40 s	12.26 s	12.17 s	12.79 s	12.62 s
9.16 s	9.15 s	9.11 s	8.42 s	8.92 d
9.08 m	9.07 d	9.02 d	8.34 d	7.77 d
8.39 d	8.35 d	8.63 s	7.80 d	7.71 d
7.98 m	7.94 d	7.90 d	7.79 d	7.70 s
7.79 d	7.79 d	7.69 d	7.75 d	7.69 d
7.58 m	7.58 t	7.55 t	7.59 t	7.54 t
7.52 m	7.51 t	7.48 t	7.55 t	7.50 t
7.44 m	7.44 t	7.40 t	7.38 t	7.41 t
7.40 m	7.40 t	7.36 t	7.31 t	7.30 t
4.09 s	4.11 s	4.08 s	4.08 s	4.08 s
^{13}C NMR spectral data				
172.1	172.4	179.8	170.6	172.9
167.5	168.0	167.5	167.8	170.0
146.7				
140.6	141.0	137.9	138.2	140.5
138.3	138.6	136.5	138.0	137.4
138.3	136.9	135.8	137.9	136.9
136.6	136.4	134.5	137.2	130.7
129.4	129.6	127.1	127.8	126.6
126.6	126.9	126.9	127.2	126.5
126.5	126.6	126.8	126.2	126.4
125.8	126.2	126.2	125.8	126.3
125.5	125.7	125.8	123.8	124.3
123.2	123.5	124.5	122.6	123.8
121.7	121.9	124.1	121.4	122.1
121.5	121.6	122.3	121.4	122.1
120.1	120.2	122.1	120.9	121.4
	119.4	121.8	119.8	118.7
114.3	114.7	121.5	119.3	115.5
114.1	114.4	120.4	116.8	113.4
112.9	113.2	112.5	113.2	112.2
112.1	112.2	111.9	113.0	111.7
52.9	52.93	53.57	53.05	53.31

δ in DMSO-d_6.

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14. Caulersin: mp >250 °C (MeOH) (lit.,[4] mp 269–270 °C, lit.,[6] mp 273–274 °C, lit.,[7] mp 352–355 °C). IR (Nujol) cm^{-1}: 3346, 3238, 1670. ^1H NMR (DMSO-d_6, 270 MHz): δ: 4.11 (3H, s, COOMe), 7.40 (1H, ddd, $J = 8.1$, 7.1, 1.0 Hz), 7.44 (1H, ddd, $J = 8.1$, 7.1, 1.0 Hz), 7.51 (1H, ddd, $J = 8.1$, 7.1, 1.0 Hz), 7.58 (1H, ddd, $J = 8.1$, 7.1, 1.0 Hz), 7.79 (1H, d, $J = 8.1$ Hz), 7.94 (1H, d, $J = 8.1$ Hz), 8.35 (1H, d, $J = 8.1$ Hz), 9.07 (1H, d, $J = 8.1$ Hz), 9.15 (1H, s, H-9), 12.26 (1H, br s, NH), 12.95 (1H, br s, NH). ^{13}C NMR (DMSO-d_6) δ: 172.4, 168.0, 141.0, 138.6, 136.9, 136.4, 129.6, 126.9, 126.6, 126.2, 125.7, 123.5, 121.9, 121.6, 120.2, 119.4, 114.7, 114.4, 113.2, 112.2, 52.9. MS *m*/*z*: 342. HRMS *m*/*z*: calcd for $C_{21}H_{14}N_2O_3$: 342.1004. Found: 342.1011.
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16. Isomer A: mp >250 °C (*n*-hexane–THF). IR ($CHCl_3$) cm^{-1}: 3333, 1698, 1617. ^1H NMR (DMSO-d_6, 270 MHz): δ 4.08 (3H, s, COOMe), 7.36 (1H, ddd, $J = 8.3$, 7.1, 1.0 Hz), 7.40 (1H, ddd, $J = 8.3$, 7.1, 1.0 Hz), 7.48 (1H, ddd, $J = 8.3$, 7.1, 1.0 Hz), 7.55 (1H, ddd, $J = 8.3$, 7.1, 1.0 Hz), 8.63 (1H, s, H-9), 9.02 (1H, d, $J = 8.3$ Hz), 9.11 (1H, d, $J = 8.3$ Hz), 12.17 (1H, br s, H-1, NH), 12.72 (1H, br s, H-1, NH). ^{13}C NMR (DMSO-d_6) δ: 178.8, 167.5, 137.9, 136.5, 135.8, 134.5, 127.1, 126.9, 126.8, 126.2, 125.8, 124.5, 124.1, 122.3, 122.1, 121.8, 121.5, 120.4, 112.5, 111.9, 53.57. MS *m*/*z*: 342. HRMS *m*/*z*: calcd for $C_{21}H_{14}N_2O_3$: 342.1004. Found: 342.1001.
17. Isomer B: mp >260 °C (MeOH). IR ($CHCl_3$) cm^{-1}: 3433, 1721. ^1H NMR (DMSO-d_6) δ: 4.08 (3H, s, OCH_3), 7.31 (1H, t, $J = 8.2$ Hz), 7.38 (1H, t, $J = 7.7$ Hz), 7.55 (1H, t, $J = 8.0$ Hz), 7.59 (1H, t, $J = 8.0$ Hz), 7.75 (1H, d, $J = 8.2$ Hz), 7.79 (1H, d, $J = 7.2$ Hz), 7.80 (1H, d, $J = 7.2$ Hz), 8.34 (1H, s), 8.42 (1H, d, $J = 8.0$ Hz), 12.79 (2H, br s, H-1 and H-1′). ^{13}C NMR δ: 170.6, 167.8, 138.2, 138.0, 137.9, 137.2, 127.8, 127.2, 126.2, 125.8, 123.8, 122.6, 121.4, 121.4, 120.9, 119.8, 119.3, 116.8, 113.2, 113.0, 53.05. MS *m*/*z*: 342. HRMS *m*/*z*: calcd for $C_{21}H_{14}N_2O_3$: 342.1005. Found: 342.0997.
18. Compound **16**: mp 221–223 °C (EtOAc). IR (Nujol) cm^{-1}: 1724, 1618. ^1H NMR ($CDCl_3$) δ: 3.74 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.59 (2H, s, CH_2), 6.81 (2H, d, $J = 8.5$ Hz), 7.02 (2H, d, $J = 8.5$ Hz), 7.32–7.72 (9H, m), 7.88 (1H, s), 8.35–8.44 (3H, m), 8.74–8.81 (1H, m).
19. Isomer C: mp >260 °C (MeOH). IR (Nujol) cm^{-1}: 3367, 3308, 1708, 1621. ^1H NMR (DMSO-d_6) δ: 4.08 (3H, s, OCH_3), 7.30 (1H, t, $J = 8.2$ Hz), 7.41 (1H, t, $J = 8.2$ Hz), 7.50 (1H, t, $J = 8.2$ Hz), 7.54 (1H, t, $J = 8.2$ Hz), 7.69 (1H, d, $J = 8.2$ Hz), 7.70 (1H, s), 7.71 (1H, d, $J = 8.2$ Hz), 7.77 (1H, d, $J = 8.2$ Hz,), 8.92 (1H, d, $J = 8.2$ Hz), 12.62 (1H, br s, NH), 12.83 (1H, br s, NH). ^{13}C NMR (DMSO-d_6) δ: 172.9, 170.0, 140.5, 137.4, 136.9, 130.7, 126.6, 126.5, 126.4, 126.3, 124.3, 123.8, 122.1, 121.4, 118.7, 115.5, 113.4, 112.2, 111.7, 53.31. MS *m*/*z*: 342. HRMS *m*/*z*: calcd for $C_{21}H_{14}O_3N_2$: 342.1005. Found: 342.1008.