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Multicomponent Synthesis of 6*H*-Dibenzo[*b,d*]pyran-6-ones and a Total Synthesis of Cannabinol

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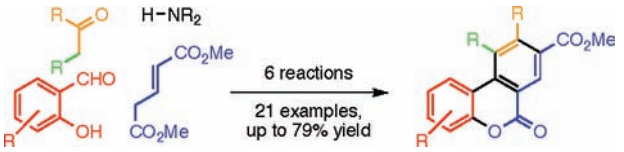
ABSTRACT



A multicomponent domino reaction that affords 6*H*-dibenzo[*b,d*]pyran-6-ones is reported. The overall transformation consists of six reactions: Knoevenagel condensation, transesterification, enamine formation, an inverse electron demand Diels–Alder (IEDDA) reaction, 1,2-elimination, and transfer hydrogenation. Both the diene and dienophile for the key inverse electron demand Diels–Alder (IEDDA) step are generated *in situ* by secondary amine-mediated processes. In most cases, the yields (10–79%) are considerably better than those obtained using a stepwise process. This methodology is employed in a concise total synthesis of cannabinol.

Multicomponent reactions (MCR) are highly valuable transformations due to their ability to incorporate three or more substrates into a single target in one operation.[1] MCRs typically achieve a substantial increase in molecular complexity and offer opportunities for diversity-oritented synthesis. They have proven to be valuable in drug discovery,[2] as well as in the total synthesis of natural products.[3]

Cannabinoids form a class of ~70 natural products that have been isolated from the plant *Cannabis sativa*.[4] Cannabinol (**1**), Δ^9-tetrahydrocannabinol (THC) (**2**), and cannabinodiol (**3**) are prominent members of this family (Figure 1). G-protein coupled cellular receptors, CB_1 and CB_2, are the targets of the cannabinoids.[5] While the CB_1 receptor is widely present in the central nervous system (CNS), especially the brain, the CB_2 receptor is less widely distributed. The CB_2 receptor is present in organs and tissues of immune-related systems, such as the spleen, thymus, bone marrow, and B lymphocytes. Hence, cannabinoid agonists that selectively bind to one of the receptors are desirable in that side effects associated with the expression of the other receptor would be minimized.[6]

Several strategies for the synthesis of cannabinol (**1**) and its derivatives have been reported. These can be classified according to the key steps involved: (1) aromatization of tetrahydrocannabinols,[7] (2) a nucleophilic aromatic substitution/lactonization/Grignard reaction sequence,[8] (3) a Suzuki coupling/lactonization/Grignard reaction sequence,[9] (4) Ru-catalyzed cyclotrimerization followed by a Grignard reaction.[10] The latter three

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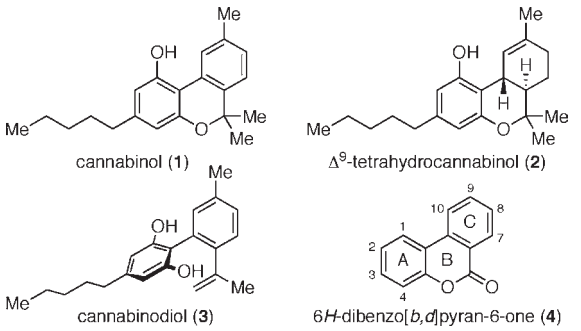
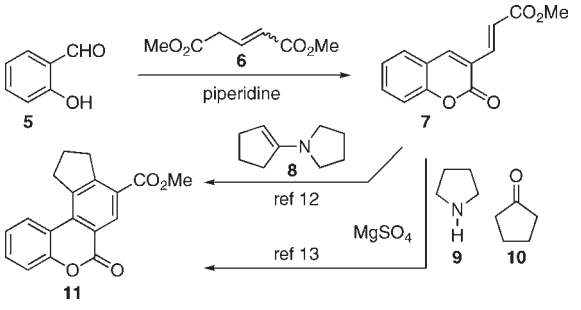


Figure 1. Prominent cannabinoids **1**–**3** and 6*H*-dibenzo[*b*,*d*]-pyran-6-one (**4**).

categories all involve the intermediacy of a derivative of 6*H*-dibenzo[*b*,*d*]pyranone (DBP) (**4**).

In connection with our ongoing studies of the inverse electron demand Diels–Alder (IEDDA) reaction,[11] our group has developed an IEDDA-based route to DBPs. In its original form, an electron-deficient diene such as **7** (the product of a reaction between salicylaldehyde (**5**) and dimethyl glutaconate (**6**)) was reacted with an enamine, e.g. **8**, to afford the corresponding DBP, e.g. **11** (Scheme 1).[12] Subsequently, it was found that an electron-rich dienophile (the enamine) could be generated *in situ* from a secondary amine and a ketone, e.g. **9** and **10**.[13] The formation of DBP **11** was explained by a domino sequence consisting of an IEDDA reaction, a 1,2-elimination of the secondary amine, and a dehydrogenation (most likely a transfer hydrogenation to a hydrogen acceptor, e.g., the enamine). This methodology was applied to the synthesis of a metabolite of ellagic acid, urolithin M7.[14]

Scheme 1. Stepwise IEDDA-Based Approaches to DBPs



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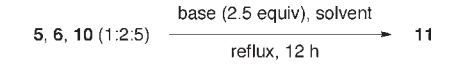
The observation that a 2° amine plays a catalytic role in both the formation of the electron-deficient diene (Knoevenagel condensation) and the electron-rich dienophile (enamine formation and subsequent elimination) prompted us to investigate the possibility of generating both IEDDA partners *in situ*.[15] If successful, this would be a multicomponent domino reaction consisting of six steps: Knoevenagel reaction, transesterification, enamine formation, IEDDA reaction, 1,2-elimination, and transfer hydrogenation. The anticipated dual catalytic function of the 2° amine presented an opportunity to perform auto-tandem organocatalysis.[16] The existence of precedence for the simultaneous *in situ* generation of both the diene and dienophile in the normal Diels–Alder reaction[15] and the application of the IEDDA reaction in MCRs[17] augured well for the success of the proposed MCR.

A mixture of salicylaldehyde (**5**), dimethyl glutaconate (**6**), and cyclopentanone (**10**) with morpholine as the base and toluene as the solvent was chosen for initial experiments. DBP **11** was obtained from the outset, and through variation of the relative amounts of the reactants and base, it was found that a maximum yield of 50% was obtained when a 1:2:5:2.5 ratio of **5**/**6**/**10**/morpholine was used. While holding this ratio constant, the solvent and base were varied (Table 1), and a maximum yield of 69% was obtained using pyrrolidine as the base and 1,4-dioxane as the solvent (Table 1, entry 10). Only with pyrrolidine as the base was any reaction at rt observed (tlc analysis). Although progress at rt was minimal, slightly better yields were obtained when reactions were first stirred at rt for 2 h before heating at reflux. Reactions conducted in 1,4-dioxane were somewhat slower than those in other solvents, so they were heated for 24 h instead of 12 h. Conditions have not yet been identified, under which substoichiometric amounts of base afford competitive yields of **11**.

Table 1. Optimization of the MCR

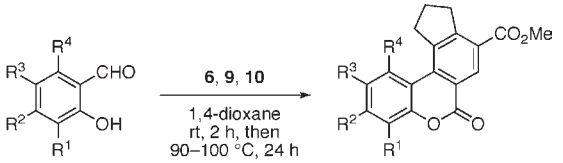


entry	base	solvent	isolated yield of **11** (%)
1	morpholine	toluene	50
2	piperidine	toluene	53
3	pyrrolidine[a]	toluene	60
4	morpholine	ethanol	54
5	L-proline	ethanol	43
6	piperidine	ethanol	57
7	pyrrolidine[a]	ethanol	56
8	morpholine	1,4-dioxane[b]	49
9	piperidine	1,4-dioxane[b]	52
10	pyrrolidine[a]	1,4-dioxane[b]	69
11	pyrrolidine[a]	chloroform	50
12	pyrrolidine[a]	tetrahydrofuran	45
13	pyrrolidine[a]	acetonitrile	58

[a] The reaction mixture was stirred at room temperature for 2 h prior to heating at reflux. [b] The reaction mixture was heated at reflux for 24 h.

Using the best conditions for the synthesis of **11**, a series of salicylaldehydes[18] was reacted with dimethyl glutaconate (**6**) and cyclopentanone (**10**) to afford a set of A-ring substituted DBPs, most of which had been previously synthesized using a stepwise approach (Table 2).[12,13] The yields ranged from 0% to 79% and, where comparisons could be made, were superior (by 1−44%, Table S1) to those obtained using stepwise syntheses.

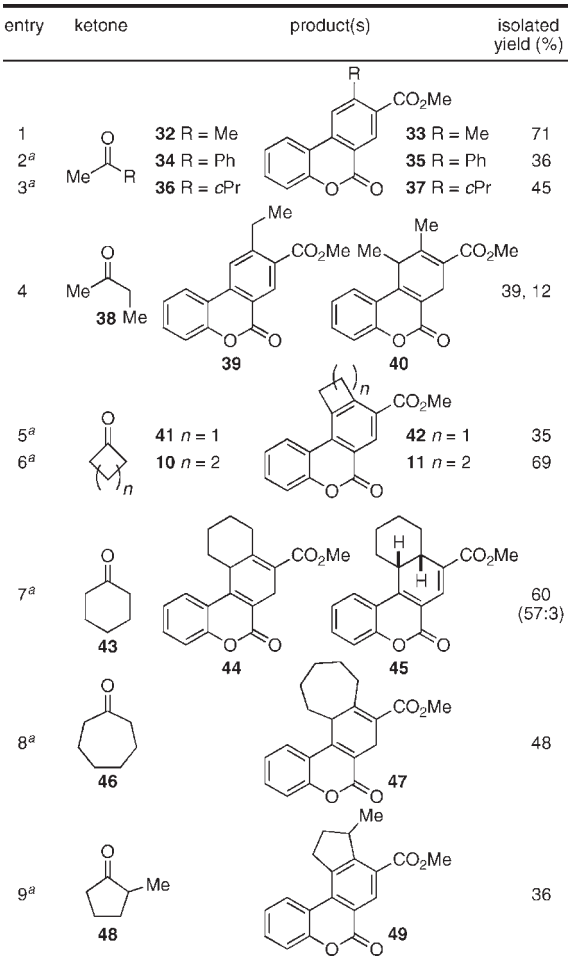
Table 2. Synthesis of A-Ring Substituted DBPs Using the MCR



entry	salicyl-aldehyde	substituent	6*H*-dibenzo-[*b*,*d*]pyran-6-one	isolated yield (%)
1	**5**	none	**11**	69
2	**12**	R^1 = OMe	**13**	57
3	**14**	R^2 = OMe	**15**	64
4	**16**	R^3 = OMe	**17**	79
5	**18**	R^4 = OMe	**19**	0
6	**20**	R^1 = Me	**21**	48
7	**22**	R^2 = Me	**23**	62
8	**24**	R^3 = Me	**25**	68
9	**26**	R^3 = Br	**27**	67
10	**28**	R^3 = CO_2Me	**29**	51
11	**30**	R^3 = NO_2	**31**	10

Only 6-methoxysalicylaldehyde (**18**) failed to afford any of the desired DBP (Table 2, entry 5). Excluding cyclopentanone (**10**) from the reaction mixture led to the formation of the corresponding methoxydiene (*cf.* **7**),[19] and it was unreactive toward *in situ* generated enamine **8**. Presumably, steric hindrance at the transition state of the cycloaddition inhibits the reaction. The other methoxy-substituted salicylaldehydes (**12**, **14**, **16**) and the corresponding methyl-substituted salicylaldehydes (**20**, **22**, **24**) reacted smoothly to afford the respective DHPs (48−79%). In both series, the yield for the 5-substituted system was the best, followed by the 4- and 3-isomers (Table 2, entries 2−4 and 6−8). For the various 5-substituted salicylaldehydes (**16**, **24**, **26**, **28**, **30**), the yields were good until the substituent became strongly electron-withdrawing (Table 2, entries 4 and 8−11). However, the drop in yield only became drastic when a nitro group was present. This is presumably due to the preferential formation of an isomeric 2*H*-chromene over the desired nitrodiene.[13]

Table 3. Synthesis of C-Ring Substituted DBPs Using the MCR



[a] 3 equiv of ketone were used instead of 5.

The ability of the MCR to generate C-ring-substituted DBPs was then probed by conducting it with a series of ketones, several of which had previously been used in stepwise DBP syntheses (Table 3).[12,13] Methyl ketones (**32**, **34**, **36**, **38**) reacted to afford the corresponding 9-substituted DBPs **33** (71%), **35** (36%), **37** (45%), and **39** (39%), respectively (Table 3, entries 1−4). In the case of butanone (**38**), nonaromatized byproduct **40** was obtained in 12% yield. This compound arises from IEDDA reaction of diene **7** with the more highly substituted enamine derived from **38**. As previously observed for systems bearing a substituent (i.e., one that is not part of a ≤5-membered fused ring) at the 10 position of the DBP skeleton, dehydrogenation did not occur.[13] However, reaction of **40** with DDQ afforded the corresponding DBP **50** in 85% yield (Scheme 2).

In line with the stepwise DBP syntheses,[12,13] small cyclic ketones (≤5-membered) **41** and **10** reacted to afford DBPs **42** (35%) and **11** (69%), whereas larger cyclic

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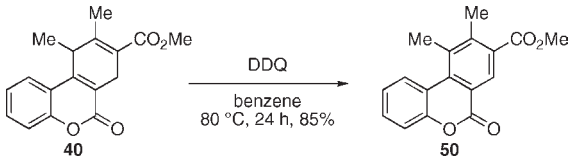
(18) Salicylaldehydes **20**, **22**, and **24** were synthesized using Skattebøl formylation: (a) Hofsløkken, N. U.; Skattebøl, L. *Acta Chem. Scand.* **1999**, *53*, 258. Salicylaldehyde **28** was synthesized using Duff formylation: (b) Duff, C. J. *J. Chem. Soc.* **1941**, 547. (c) Lindoy, L. F.; Meehan, G. V.; Svenstrup, N. *Synthesis* **1998**, 1029. The remaining salicylaldehydes were purchased.

(19) This diene was obtained as a *ca.* 1:1 mixture with an unidentified byproduct.

Scheme 2. Synthesis of DBP **50**

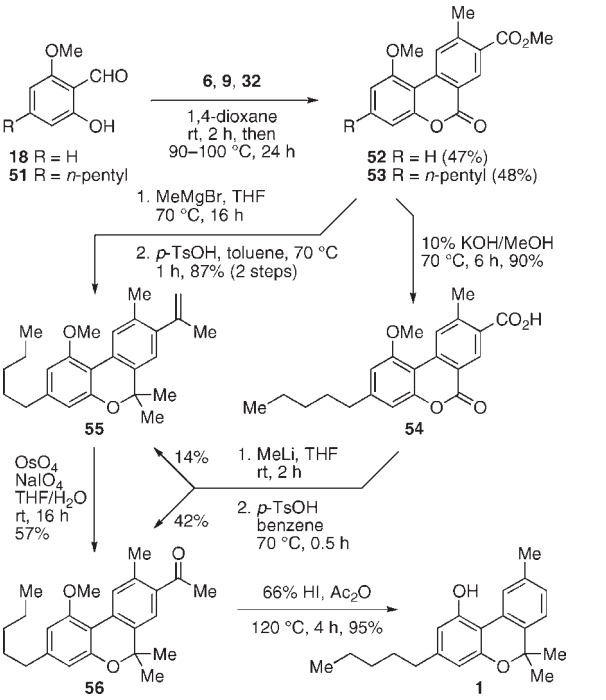


ketones (≥6-membered) **43** and **46** afforded nonaromatized products (Table 3, entries 5−8). Cyclohexanone (**43**) gave a mixture of cyclohexadienes **44** and **45** (60% combined, 57:3 by ^{1}H NMR analysis), and cycloheptanone (**46**) gave only 1,4-cyclohexadiene **47** (48%). The aromatization of **44**/**45** and **47** using DDQ was reported earlier.[13] 2-Methylcyclopentanone (**48**) afforded only DBP **49**, which arises from reaction of the less substituted enamine (Table 3, entry 9). Where comparisons are available, the yields of the MCR are mostly better than those of the corresponding stepwise syntheses (Table S2). Exceptions are acetophenone (**34**), cyclohexanone (**43**), and cycloheptanone (**46**).

6-Methoxysalicylaldehyde (**18**), which had failed to afford DBP **19** in an MCR with cyclopentanone (**10**), reacted with **6** and acetone (**34**) to provide DBP **52** (47%) (Scheme 3). The MCR clearly tolerates one substituent, but not two, in the bay region of the DBP framework.

Salicycladehyde **51**[20] also reacted well with **6** and **32**, affording DBP **53** (48%) on a 1.2 g scale. This product was converted into cannabinol (**1**) by two different four-step pathways (Scheme 3). Hydrolysis of **53** afforded acid **54** (90%). Treatment of **54** with MeLi (8 equiv), followed by reaction of the crude product with *p*-TsOH, brought about simultaneous conversion of the acid group to a methyl ketone and the pyranone system to a dimethylpyran unit. Alkene **55** (14%) was consistently obtained along with the intended product **56** (42%). Alternatively, alkene **55** could be accessed by a Grignard reaction of **53** with MeMgBr, followed by treatment of the crude product with *p*-TsOH (87%, 2 steps). Oxidative cleavage of the terminal alkene then afforded methyl ketone **56** (57%). The synthesis of cannabinol (**1**) was then completed by reacting **56** with HI/Ac_2O, which effected both demethylation and deacylation in high yield (95%). This seldom-used

Scheme 3. Synthesis of Cannabinol (**1**)



retro-Friedel−Crafts acylation relies upon the presence of an adjacent methyl group.[21]

In conclusion, previously reported stepwise syntheses of DBPs have been combined to afford a multicomponent domino reaction that performs substantially better than the stepwise approaches in most cases. Six reactions (Knoevenagel reaction, transesterification, enamine formation, IEDDA reaction, 1,2-elimination, transfer hydrogenation) occur during the MCR, in which both IEDDA components are generaterd *in situ* and pyrrolidine mediates two separate processes (Knoevenagel reaction and enamine formation). This chemistry has been applied in the total synthesis of cannabinol (**1**).

Acknowledgment. Financial support of this work from the Natural Sciences and Engineering Research Council (NSERC) of Canada is gratefully acknowledged.

Supporting Information Available. Experimental procedures and characterization data. ^{1}H and ^{13}C NMR spectra. Tables of yields for stepwise and multicomponent syntheses of DBPs. This material is available free of charge via the Internet at http://pubs.acs.org.

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