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RESEARCH ARTICLE

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Versatile Solid-Phase Synthesis of Chromenes Resembling Classical Cannabinoids

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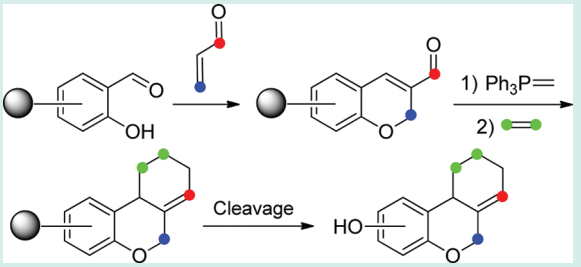
Supporting Information

ABSTRACT: A novel solid-phase approach toward classical cannabinoids is described. The desired tricyclic natural product analogues are assembled in only four atom economic steps: domino oxa-Michael-aldol condensation, Wittig reaction/enol-ether formation, Diels−Alder cycloaddition and cleavage. The synthesis is designed to allow combinatorial chemistry at several stages of the sequence. The variation of commercially available reagents at three of the reactions (enals/enones, Wittig salts, and dienophiles) allows the introduction of various diversity points. As proof of concept, a small library of 20 members has been synthesized with overall yields ranging from 10% to 60%.



KEYWORDS: cannabinoids, combinatorial chemistry, domino reactions, heterocycles, natural products, solid phase synthesis

INTRODUCTION

Classical cannabinoids are a group of approximately 70 terpenophenolic secondary metabolites produced by Indian hemp (*Cannabis sativa* var. *indica*). The most prominent of these psychotropic compounds is (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC, Dronabinol, **1**, Figure 1), which was isolated by Gaoni and Mechoulam in 1964[1] and bears a tricyclic 6*a*,7,8,10*a*-tetrahydro-6*H*-benzo[*c*]chromene core structure.

Δ^9-THC and other cannabinoids have been used in medicine since the 1980s to treat symptoms of cancer, pain relief, and spasticity in multiple sclerosis, or as appetite stimulants for AIDS patients.[2] Furthermore, they alleviate nausea and vomiting during chemotherapy and are commercially available under the trademark names of Sativex, Marinol, or Cesamet.

The physiological activities of THC and other cannabinoids are based on their interaction with certain membrane bound G-protein coupled cannabinoid receptors. So far two of these, CB_1 and CB_2, have been confirmed.[3] CB_1-receptors are primarily found in the brain with the highest concentrations in the basal ganglia, cerebellum, and the limbic system, including the hippocampus. Interaction of THC with the CB_1 receptor causes the euphoric and anticonvulsive effects of cannabis. CB_2-receptors are almost exclusively located in the immune system, with the greatest density in the spleen. They are responsible for anti-inflammatory and other therapeutic activities.

The aim of this work is to generate a library of novel THC-analogous structures, which will subsequently be tested for their biological activity (e.g., interaction with CB-receptors). The identification of receptor-selective compounds will serve to minimize the adverse effects of existing drugs, such as their addictive or psychotropic properties. Furthermore, the synthesis of diversely modified THC-like molecules will allow to explore the full therapeutic potential of cannabinoids, which ranges from Parkinson's disease and Huntington disease up to obesity and drug dependence treatment.[2e,4]

THC and several analogous cannabinoid compounds have already been prepared synthetically.[5] But the methods employed are usually quite rigid concerning modifications of the side chains, limiting the availability of a broad range of derivatives. To circumvent this problem, a new strategy toward the generation of cannabinoids is proposed here: combinatorial chemistry on solid supports. It is not only compatible with various substitution patterns, but also avoids extensive purification and will allow automation later on.

RESULTS AND DISCUSSION

Our approach is designed to yield diverse THC-analogues in a straightforward, four-step reaction sequence. It starts by reacting salicylaldehyde (SA) motif bearing molecules attached to a polystyrene backbone with various Michael acceptors in a domino oxa-Michael-aldol (DOMA) condensation (Figure 2).[6]

The formed 2*H*-chromene-3-carbaldehydes are then treated with Wittig salts or are converted into enol-ethers, yielding in both cases dienes of a different reactivity pattern. The diene moieties are later on subjected to a Diels−Alder cycloaddition

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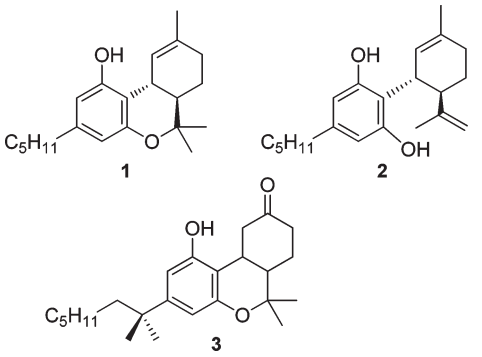


Figure 1. Cannabinoids in clinical use: Dronabinol (**1**), Cannabidiol (**2**), Nabilone (**3**).

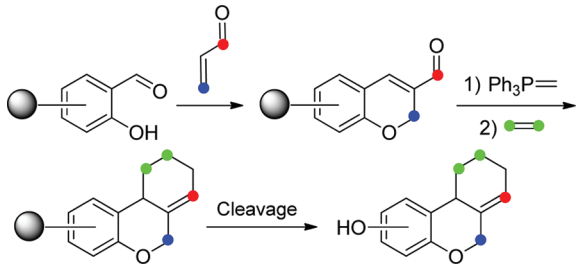


Figure 2. General approach to THC-like structures; introduction of diversity points.

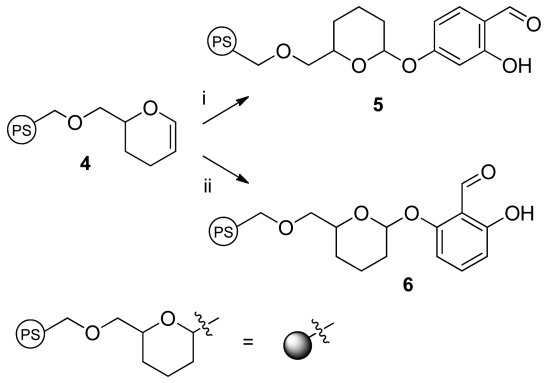
with dienophiles, concluding the route to the tricyclic structures typical for classical cannabinoids.

Our first approach was to immobilize the commercially available 4-hydroxysalicylaldehyde (4-HSA) directly on Merrifield resin.[7] Neither treatment in 10% nor 50% TFA in CH_2Cl_2 released any of the attached material. Harsher conditions were not employed, as they would limit the number of possible functionalities to be introduced later on. The same result was found for Wang resin.[8] Attachment and cleavage with Ellman's acid-labile DHP-linker (**4**) was finally successful (Scheme 1).[9]

Compared to other linkers, such as the triazene one for coupling of aniline-precursors,[10] it did not require protection of the HSAs used as starting material and could be easily prepared by etherification of Merrifield resin[7] (0.99 mmol/g).[11] At first, polymer **4** was treated with 4-HSA/PPTS (pyridinium *p*-toluenesulfonate) to give resin **5** in a yield of up to 48% (0.43 mmol/g) under optimized conditions (determined via cleavage from solid supports). In addition, 6-HSA[11] was immobilized in 52% yield (0.46 mmol/g, **6**, Scheme 1).

To generate the chromene core structure the conditions for the DOMA condensation[6] were optimized for resin **5** and acrolein as Michael acceptor. Although there is literature precedence for solid phase syntheses of chromenes,[12] the method reported herein is to the best of our knowledge the first domino reaction with SAs on solid supports.[6a,13] Mixtures of 1,4-dioxane or tetrahydrofuran (THF) with water for better solubility of the base (DABCO, Na_2CO_3 or K_2CO_3) were explored. Nevertheless only traces of product were formed under conventional heating or ultrasound. The same was found for other basic conditions displaying good results in solution phase (*N*-methylimidazole, tetramethylguanidine,[14a] or pyrrolidine/benzoic acid[14b]). Finally, by employing K_2CO_3 in 1,4-dioxane with agitation at 80 °C for

Scheme 1. Immobilization of SAs on Resin 4[a]



[a] Reaction conditions: (i) 4-HSA, PPTS, DCE/toluene, 55 °C, 16 h. (ii) 6-HSA, PPTS, DCE/toluene, 55 °C, 16 h.

4 days, chromene **8**{*1*} was obtained in 65% yield (Scheme 2; Table 1, Entry 1; data from [ref 6a] are included).[15]

Degassing of the solvent turned out to be crucial for the reproducibility of the experiments. According to these conditions, resin **5** was reacted with four other Michael acceptors (Figure 3), resulting in chromenes **8** in yields between 38−90% (Table 1, Entries 2−5). In all cases, except for entry 4, the purity of the products after cleavage was above 90%, as determined by ^{1}H NMR of the reactions after workup. The lower yields are probably due to prior cleavage from the resin during the DOMA condensation.

When switching to resin **6** and acrolein as Michael acceptor, the reaction would not proceed to completion. After repeating the DOMA condensation twice with the same batch of resin, the ratio of product to starting material remained at 4:1, explaining the yield of only 32% (Table 1, Entry 6). A similar result was found for crotonaldehyde (**7**{*3*}) (Entry 7). When switching to senecialdehyde (**7**{*2*}), no product could be found after cleavage, only 30% of side-product **15** formed by a vinylogous aldol condensation were isolated.[6c,16] Apparently, the DOMA condensation is dependent on the substitution pattern of the aromatic ring and does not tolerate immobilization on position 6 very well.

To compare the results above with an analogous solution phase approach,[17] THP-protected HSAs **10**+**12** and reagents **7**{*1*−*3*+*5*} were also subjected to the DOMA condensation.[18] With the exceptions of acrolein and methyl vinyl ketone **7**{*1*+*5*}, lower yields were observed for compound **10** substituted in position 4 (Table 1, Entries 9−12). Furthermore, the resulting chromenes **11** were contaminated with many side-products that were difficult to separate. In case of substrate **12**, the same trend as in solid phase could be observed: lower yields for substitution in position 6 and formation of side-product **14b** with senecialdehyde (Entries 13 + 14). In conclusion, the solid phase approach was found to be more effective, especially for sterically demanding Michael acceptors. This is probably due to the high actual excess of reagents,[17] a feature predestined for solid phase chemistry because of their ease of separation by filtration.

Because of the suboptimal results for the DOMA condensation with resin **6** and the consecutive low loading of **9**, the sequence was only continued with resins **8** immobilized in position 4. The next step was either Wittig reaction with CH_3PPh_3Br[19] to **16**{*1*+*2*} or TBS-enol ether formation yielding **18**{*5*} (Scheme 3, left).

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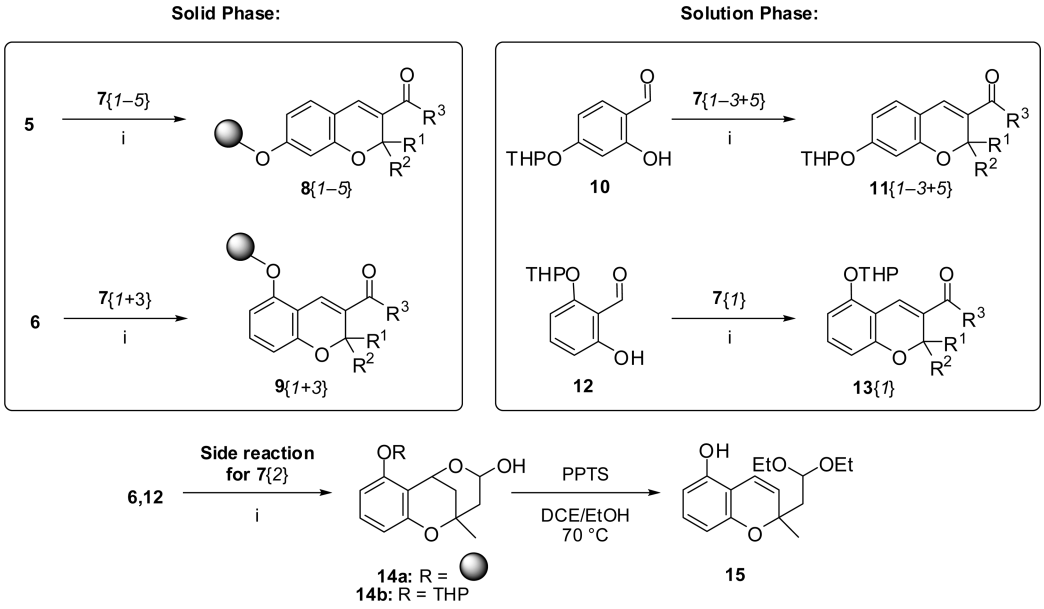
Scheme 2. DOMA: Solid and Solution Phase[a,b]



[a] Reaction conditions: (i) K_2CO_3, 1,4-dioxane, 80 °C, 4 d. [b] For R^1, R^2, R^3 see Table 1.

Table 1. Yields for the DOMA Condensation: Solid and Solution Phase

entry	substrate	product	R^1	R^2	R^3	yield (%)
1[6a]	**5**	**8**{*1*}	H	H	H	65[a]
2[6a]	**5**	**8**{2}	Me	Me	H	85[a,b]
3[6a]	**5**	**8**{*3*}	Me	H	H	90[a]
4	**5**	**8**{*4*}	Ph	H	H	38[a,c]
5	**5**	**8**{*5*}	H	H	Me	50[a]
6[6a]	**6**	**9**{*1*}	H	H	H	32[a]
7[6a]	**6**	**9**{*3*}	Me	H	H	27[a]
8[6a]	**6**	**15**				25[a]
9[6a]	**10**	**11**{*1*}	H	H	H	89[d]
10[6a]	**10**	**11**{2}	Me	Me	H	44[d]
11[6a]	**10**	**11**{3}	Me	H	H	75[d]
12	**10**	**11**{*5*}	H	H	Me	67[d]
13[6a]	**12**	**13**{*1*}	H	H	H	43[d]
14[6a]	**12**	**14b**				69[d]

[a] Average isolated yield after cleavage (reproducible within a 10% yield range). [b] Formation of 5−10% of the vinylogous aldol condensation product, not isolated. [c] Additionally, 27% of starting material were recovered. [d] Isolated yield.

Again, analogous solution phase syntheses were performed,[17] giving **17**{*1+2*} and **19**{*5*} in 80, 87, and 73% yield, respectively. In all three cases the resulting products were not stable in pure form and dimerized within days in the refrigerator. Accordingly, the yields of the solid phase approach were not determined by cleavage reaction, but by Raman spectroscopy (Scheme 3, right-hand side). Complete disappearance of the carbonyl bands from the starting materials (blue) compared to the products (red) allowed an assignment of quantitative conversion. Furthermore, resins **16**{*1+2*} were unable to dimerize because of being immobilized, resulting in far greater stability (>1 month at room temperature (r.t.)), a further reason for choosing the solid phase approach over the solution one.

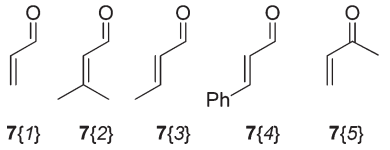


Figure 3. Diversity reagents for the DOMA condensation 7{*1*−*5*}.

For the Diels−Alder reaction, thermal conditions (80 °C) were chosen, as Lewis or Brønsted acid catalysis would lead to concomitant cleavage from the resin (Scheme 4).

Initially, the reaction of **16**{*1*} with methyl vinyl ketone (**20**{*1*}) as dienophile was screened in different solvents (toluene, DMF, DCE). This resulted in comparable, almost quantitative yields, but the best *endo*/*exo* ratios were observed with toluene, making it the solvent of choice (Table 2, Entry 1).

Resin **16**{*1*} was reacted with two further dienophiles (Entries 2 + 3). But more emphasis was paid to resin **16**{*2*} (R^1 = R^2 = Me) because of its higher loading and greater similarity to THC. It was converted to 12 different products **21**{*2,1*−*12*} with all diversity reagents **20** shown in Figure 4. For both dienes no general trend concerning the selectivity of the Diels−Alder reaction could be observed. It ranged from exclusively *endo* (maleimides **20**{*7* + *8*}, Entries 10 + 11, 19) to mainly *exo* in case of acrylonitrile (**20**{*3*}, Entry 6). Usually, diastereomeric mixtures favoring the *endo*-product were formed, which could be separated by column chromatography in almost all cases. This was more of an advantage, as a higher number of compounds for later testing could be generated. In case of methyl vinyl ketone as dienophile (Entry 4), the lower yield and increased *exo*-ratio was caused by the *endo*-diastereomer being labile (starting decomposition after a few hours in the NMR tube). Generally, the *endo*-products were more prone to decomposition compared to the thermodynamically more stable *exo* ones.

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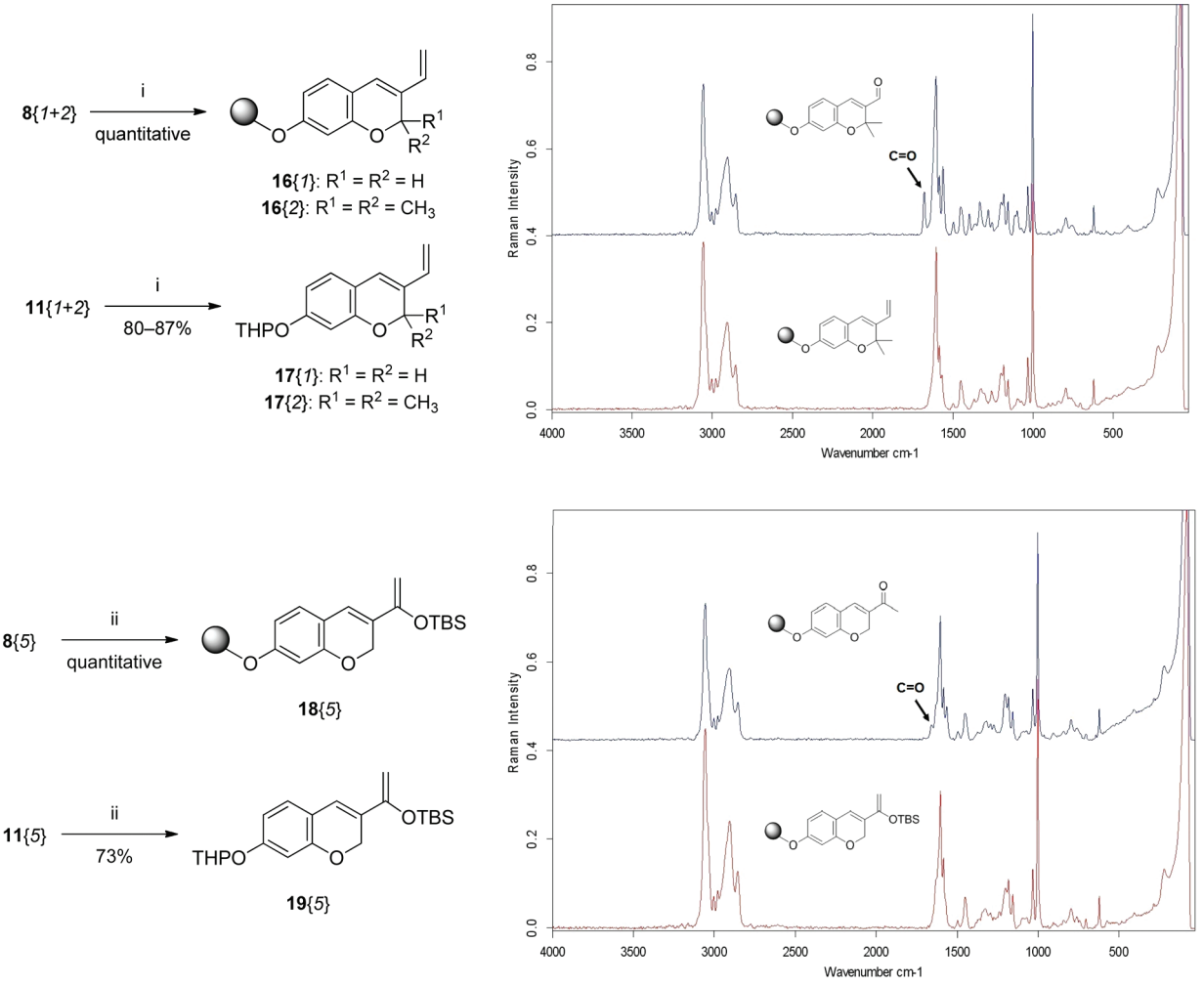
Scheme 3. Wittig Reaction and Enol-Ether Formation, Including Raman Spectra[a]



[a] Reaction conditions: (i) CH_3PPh_3Br, *n*-BuLi, THF, −35 °C to r.t., 2 h. (ii) Et_3N, TBSOTf, CH_2Cl_2, −30 °C to r.t., 16 h.

Worth mentioning are compounds **21**{*2,11 + 12*} formed from diazocarboxylates, as such heterocyclic dihydrochromenopyridazines have not been investigated concerning the CB receptors so far (entries 14 + 15).[20]

Next, enol ether **18**{*5*} was subjected to the Diels−Alder reaction (Scheme 5, Entries 16−20).

The resulting tricycles **22** were at first cleaved with PPTS in DCE/EtOH giving ketones **24** directly under concomitant loss of the TBS-group (Entries 16−17). Unfortunately, the yield was reduced because of diethyl acetal **25** being formed as a side-product. When switching the solvent to THF/water, the formation of **25** was avoided, but now the TBS group was only partially cleaved-off, mainly giving enol-ethers **23**. Further treatment with TBAF in acetonitrile finally liberated tricycles **24** in all cases except for **23**{*5,11*}, where side-product **26**{*5,11*} was formed exclusively. The latter also occurred for other dienophiles (see footnotes f, g, i in Table 2) in 7−15% yield independent of the cleavage conditions. In all cases, the stereochemistry of the hydrogen atoms on the carbons of the former double bond was *anti* after isomerization from enol-ethers to the ketones.

In conclusion, a combinatorial approach toward THC-like molecules has been developed, proven by the synthesis of a library with 20 structurally different members. Almost twice this amount is available for testing, when including diastereomers and tricyclic side-products. The chromene cannabinoids are formed in up to 60% yield employing a four step solid phase synthesis. The best suited starting material is 4-HSA immobilized on Merrifield resin via a THP-linker. The route itself is open to various substitution patterns, which can simply be introduced by variation of the starting material or reagents. The latter are cheap and commercially available (Michael acceptors, Wittig salts, dienophiles).

Our solid phase approach has several advantages compared to one in solution: higher yields because of excess of reagents, increased stability of the intermediates (no decomposition by dimerization possible), plus the possibility for automation.

In the future, the latter will be exploited to explore the full potential of structural diversity. The generated library of substrates will then be tested toward affinity for the cannabinoid receptors.

EXPERIMENTAL PROCEDURES

General Procedure for Immobilization. DHP-resin **4** (6 g, 0.99 mmol/g) was dried overnight at 100 °C, then suspended in a

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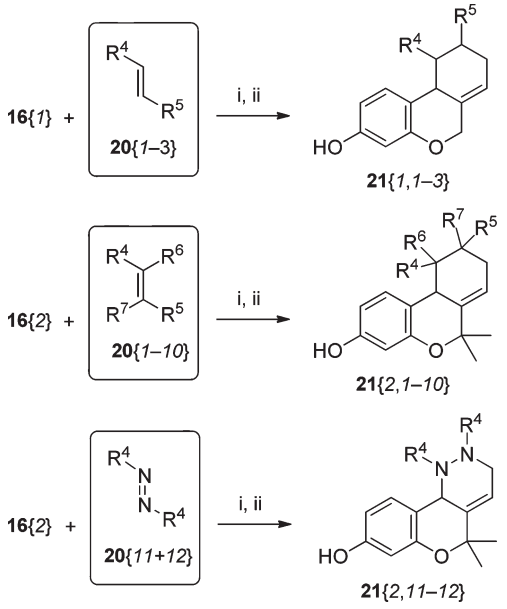
Scheme 4. Diels–Alder Cycloaddition and Cleavage[a]



[a] Reaction conditions: (i) Toluene, 80 °C, 2 d. (ii) PPTS, DCE/EtOH, 65 °C, 16 h.

mixture of DCE/toluene (42/18 mL) under nitrogen. 4- or 6-HSA (4.15 g, 30.0 mmol) and PPTS (2.26 g, 9.00 mmol) were added, and the mixture agitated at 55 °C overnight. Afterward, the resin was filtered, washed (CH_2Cl_2, 2 × H_2O and DMF, 2 × H_2O and THF, 3 × MeOH and CH_2Cl_2, 4 × CH_2Cl_2; with 20 mL/g resin each), and dried under vacuum.

General Procedure for Cleavage. A 200 mg portion of the resin was suspended in a 1:1 mixture of EtOH/DCE (4 mL) or a

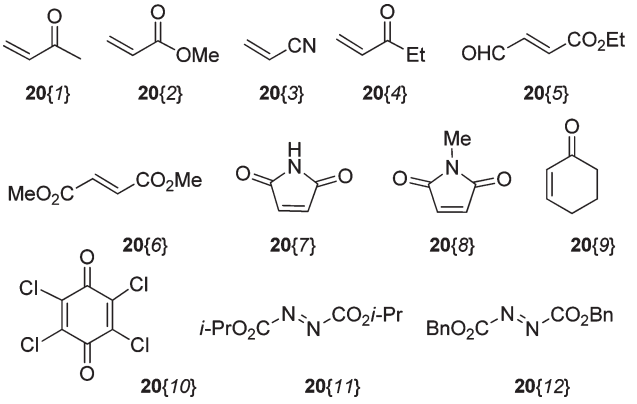


Figure 4. Diversity reagents for the Diels–Alder cycloaddition **20**{*1–12*}.

Table 2. Yields for the Diels–Alder Cycloaddition

entry	substrate	dienophile	product	$R^1 = R^2$	R^4	R^5, R^6	R^7	*endo*/*exo*[a]	yield[b] (%)
1[6a]	**16**{*1*}	**20**{*1*}	**21**{*1,1*}	H	C(O)Me	H, H	H	4/1	95
2[6a]	**16**{*1*}	**20**{*2*}	**21**{*1,2*}	H	CO_2Me	H, H	H	2/1	90
3[6a]	**16**{*1*}	**20**{*3*}	**21**{*1,3*}	H	CN	H, H	H	4/5	50,
4	**16**{*2*}	**20**{*1*}	**21**{*2,1*}	CH_3	C(O)Me	H, H	H	7/10	50
5	**16**{*2*}	**20**{*2*}	**21**{*2,2*}	CH_3	CO_2Me	H, H	H	1/1	35
6[6a]	**16**{*2*}	**20**{*3*}	**21**{*2,3*}	CH_3	CN	H, H	H	1/10	50
7[6a]	**16**{*2*}	**20**{*4*}	**21**{*2,4*}	CH_3	C(O)Et	H, H	H	8/5	70
8[6a]	**16**{*2*}	**20**{*5*}	**21**{*2,5*}	CH_3	CO_2Me	CO_2Me, H	H	1/1	32
9	**16**{*2*}	**20**{*6*}	**21**{*2,6*}	CH_3	CHO	CO_2Et, H	H	5/4	29[c]
10	**16**{*2*}	**20**{*7*}	**21**{*2,7*}	CH_3	H	C(O)N(H)C(O)	H	1/0	23
11	**16**{*2*}	**20**{*8*}	**21**{*2,8*}	CH_3	H	C(O)N(Me)C(O)	H	1/0	27
12	**16**{*2*}	**20**{*9*}	**21**{*2,9*}	CH_3	H	$C(O)CH_2CH_2CH_2$	H		Traces[d]
13	**16**{*2*}	**20**{*10*}	**21**{*2,10*}	CH_3	Cl	$C(O)(CCl)_2C(O)$	Cl	1/1	11[e]
14[6a]	**16**{*2*}	**20**{*11*}	**21**{*2,11*}	CH_3	CO_2i-Pr	CO_2i-Pr			30
15	**16**{*2*}	**20**{*12*}	**21**{*2,12*}	CH_3	CO_2Bn	CO_2Bn			48
16	**18**{*S*}	**20**{*1*}	**24**{*S,1*}	H	C(O)Me	H, H	H	1/2	35[f]
17	**18**{*S*}	**20**{*2*}	**24**{*S,2*}	H	CO_2Me	H, H	H	2/1	51[g]
18	**18**{*S*}	**20**{*3*}	**23**{*S,3*}	H	CN	H, H	H		15[h]
			24{*S,3*}					0/1	10[h]
19	**18**{*S*}	**20**{*8*}	**23**{*S,8*}	H	H	C(O)NMeC(O)	H	1/0	20[i]
			24{*S,8*}					4/5	12[i]
20	**18**{*S*}	**20**{*11*}	**23**{*S,11*}	H	CO_2i-Pr	CO_2i-Pr			20[j]
			24{*S,11*}						8[j]

[a] Determined by ^{1}H NMR of the crude product. All diastereomers apart from **21**{*2,5*}and **21**{*2,10*} were separable by column chromatography. [b] Average isolated yield of *endo*- and *exo*-diastereomers after cleavage if not otherwise mentioned. [c] Cleavage in DCE/ethanol resulted in acetal formation of the aldehyde, which was removed by the addition of *p*-TsOH. The isolated yield was 16% of the *endo*-isomer, but according to NMR of the crude product 13% of the *exo*-isomer were formed as well, which were lost upon chromatography. [d] Complex mixture after slow conversion, the main component being the dimer of the Wittig product. [e] Formation of 10% of a side product with an aromatized C-ring. [f] Cleavage in DCE/ethanol gives additionally 15% of **26**{*S,1*} and 20% of starting material (DOMA-product). [g] Cleavage in DCE/ethanol gives additionally 22% of **25**{*S,1*}, 7% of **26**{*S,1*} and 20% of the DOMA-product. [h] Cleavage in THF/water gives additionally 8% of the DOMA-product. [i] Cleavage in THF/water gives additionally 10% of **26**{*S,8*}. [j] Cleavage in THF/water gives additionally 13% of the DOMA-product.

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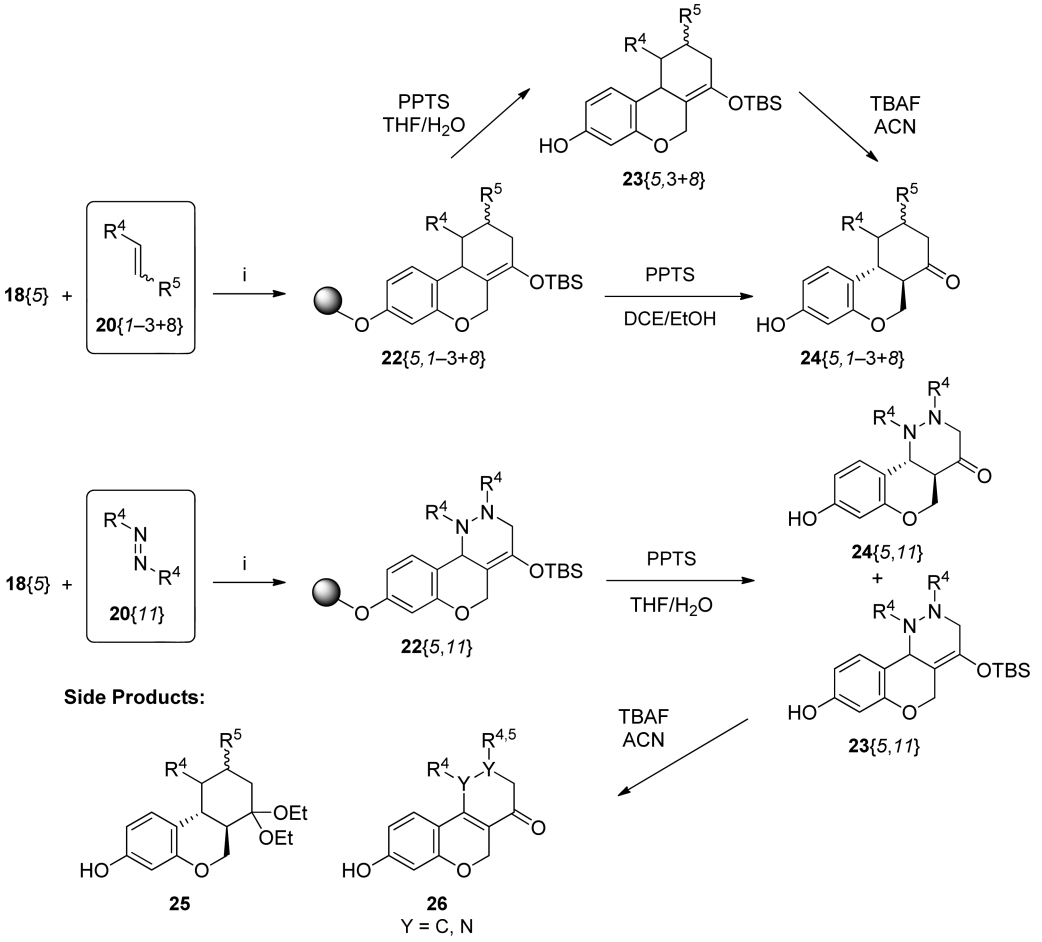
Scheme 5. Diels−Alder Cycloaddition of TBS-Enol Ether 18{*5*}[a]



[a] Reaction conditions: (i) Toluene, 80 °C, 2 d.

6:1 mixture of THF/water (4 mL) in case of the enol-ether path to avoid acetal formation of the resulting ketone. Then PPTS (100 mg, 0.400 mmol) was added, and the mixture was agitated at 65 °C overnight. The resin was separated by filtration, washed with 25 mL of EtOAc, and the filtrate concentrated. The crude product was diluted with EtOAc (15 mL) and water (10 mL). The organic layer was separated, and the aqueous one extracted twice with EtOAc (15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. After Diels−Alder reactions the crude products were additionally purified by flash chromatography to separate *endo*- and *exo*-diastereomers.

General Procedure for DOMA Condensation. A 1.00 g portion of the resin (**5** or **6**) was suspended in 1,4-dioxane (10 mL) in a 20 mL vial. Nitrogen was bubbled through for a few minutes, before adding K_2CO_3 (552 mg, 4.00 mmol) and the Michael acceptor (6.0 mmol). The vial was closed and agitated at 80 °C for 4 d. After the second day another portion of the Michael acceptor (1.00 mmol) was added. At the end of the reaction, the resin was filtered, washed (as described above) and dried under vacuum. The procedure was repeated a second time if remaining starting material was detected after cleavage.

General Procedure for Enol-Ether Formation. A 2.50 g portion of resin **8** was dissolved in CH_2Cl_2 (25 mL) and flushed with nitrogen for 5 min. Et_3N (2.08 mL, 1.52 g, 15.0 mmol) was added, followed by TBSOTf (1.70 mL, 1.98 g, 7.50 mmol) at −30 °C. Afterwards, the reaction was agitated for 16 h, in which the temperature was allowed to rise to r.t. The resin was separated by filtration, washed (as described above), and dried under vacuum.

General Procedure for Wittig Reaction. Methyl triphenylphosphonium bromide (1.79 g, 5.00 mmol) was suspended in dry THF (14 mL) under nitrogen and cooled to −25 °C. *n*-BuLi (3.1 mL, 5.0 mmol, 1.6 M solution in hexanes) was added (yellow color), and the mixture stirred for 2 h (−25 °C up to r.t.). Afterward, it was cooled to −35 °C and added to resin **8** (1.65 g), which was previously suspended in 12 mL of dry THF, also cooled to −35 °C. The reaction was allowed to warm up to r.t. over the next 2 h. It was then quenched with water (2 mL), washed (as described above), and dried under vacuum.

General Procedure for Diels−Alder Reaction. Resins **16** and **18** (500 mg) were dried overnight at 90 °C. They were suspended in toluene (5 mL) in separate vials and nitrogen was bubbled through for 10 min. The dienophile (5.0 mmol) was added in each vial, the vials closed, and the reaction agitated at 80 °C for 2 days. The resins were filtered, washed (as described above), and dried under vacuum before being cleaved.

■ ASSOCIATED CONTENT

Supporting Information. Experimental procedures are given, including the preparation of starting materials (**6-HSA**, **10**, **12**),

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analogous solution phase syntheses, characterization of all compounds, as well as selected gel-^{13}C NMR spectra (**4**, **5**, **6**, **8**{*1*−*3*}, **16**{*1*−*2*}), Raman spectra (**8**{*1*−*2*}, **16**{*1*−*2*}, **18**{*5*}), and ^{1}H/^{13}C NMR spectra of representative library members (**21**{*1,3*}, **21**{*2,2*}, **21**{*2,3*}, **21**{*2,7*}, **21**{*2,10*}, **21**{*5,3*}). This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

D.C.K. and S.B. conceived and designed the project, as well as co-wrote the manuscript. D.C.K. performed the experimental work.

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ABBREVIATIONS

DABCO, 1,4-diazabicyclo[2.2.2]octane; DCE, 1,2-dichloroethane; DOMA, domino oxa-Michael-aldol; HSA, hydroxyl-salicylic acid; PPTS, pyridinium *p*-toluenesulfonate; SA, salicylaldehyde; TBAF, tetrabutylammonium fluoride; TBSOTf, *t*-butyldimethylsilyl trifluoromethanesulfonate; THC, tetrahydrocannabinol; *p*-TsOH, *p*-toluenesulfonic acid

REFERENCES

(1) Gaoni, Y.; Mechoulam, R. Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish. *J. Am. Chem. Soc.* **1964**, *86*, 1646–1647.

(2) (a) Sarfaraz, S.; Adhami, V. M.; Syed, D. N.; Afaq, F.; Mukhtar, H. Cannabinoids for Cancer Treatment: Progress and Promise. *Cancer Res.* **2008**, *68*, 339–342. (b) Ware, M. A.; Daeninck, P.; Maida, V. A review of nabilone in the treatment of chemotherapy-induced nausea and vomiting. *Ther. Clin. Risk Manage.* **2008**, *4*, 99–107. (c) Pertwee, R. G. Cannabinoids and Multiple Sclerosis. *Mol. Neurobiol.* **2007**, *36*, 45–59. (d) Mackie, K. Cannabinoid Receptors as Therapeutic Targets. *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 101–122. (e) Romero, J.; Lastres-Becker, L.; de Miguel, R.; Berrendero, F.; Ramos, J. A.; Fernandez-Ruiz, J. The endogenous cannabinoid system and the basal ganglia: biochemical, pharmacological, and therapeutic aspects. *Pharmacol. Ther.* **2002**, *95*, 137–152.

(3) Reviews: (a) Poso, A.; Huffman, J. W. Targeting the cannabinoid CB2 receptor: modelling and structural determinants of CB2 selective ligands. *Br. J. Pharmacol.* **2008**, *153*, 335–346. (b) Svíženská, I.; Dubový, P.; Šulcová, A. Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures − A short Review. *Pharmacol., Biochem. Behav.* **2008**, 501–511. (c) Howlett, A. C.; Barth, F.; Bonner, T. I.; Cabral, G.; Casellas, P.; Devane, W. A.; Felder, C. C.; Herkenham, M.; Mackie, K.; Martin, B. R.; Mechoulam, R.; Pertwee, R. G. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol. Rev.* **2002**, *54*, 161–202.

(4) (a) Akbas, F.; Gasteyger, C.; Sjödin, A.; Astrup, A.; Larsen, T. M. A critical review of the cannabinoid receptor as a drug target for obesity management. *Obes. Rev.* **2009**, *10*, 58–67. (b) Le Foll, B.; Forget, B.; Aubin, H.-J.; Goldberg, S. R. Blocking cannabinoid CB_1 receptors for the treatment of nicotine dependence: insights from pre-clinical and clinical studies. *Addict. Biol.* **2008**, *13*, 239–252.

(5) (a) Burdick, D.; DeOrazio, R.; Guzzo, P.; Habershaw, A.; Helle, M.; Paul, B.; Wolf, M. Synthesis and structure-activity relationship of substitutions at the C-1 position of (−)-Δ^9-tetrahydrocannabinol. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1424–1426. (b) Trost, B. M.; Dogra, K. Synthesis of (−)-Δ^9-*trans*-Tetrahydrocannabinol: Stereocontrol via Mo-Catalyzed Asymmetric Allylic Alkylation Reaction. *Org. Lett.* **2007**, *9*, 861–863. (c) Sun, H.; Mahadevan, A.; Razdan, R. K. A novel methodology for the synthesis of Δ^8-tetrahydrocannabinol (THC) analogues. *Tetrahedron Lett.* **2004**, *45*, 615–617. (d) Chu, C.; Ramamurthy, A.; Makriyannis, A.; Tius, M. A. Synthesis of Covalent Probes for the Radiolabeling of the Cannabinoid Receptor. *J. Org. Chem.* **2003**, *68*, 55–61. (e) Liddle, J.; Huffman, J. W. Enantioselective synthesis of 11-hydroxy-(1′*S*,2′*R*)-dimethylheptyl-Δ^8-THC, a very potent CB1 agonist. *Tetrahedron* **2001**, *57*, 7607–7612. (f) Tietze, L. F.; Kettschau, G.; Gewert, J. A.; Schuffenhauer, A. Hetero-Diels-Alder reactions of 1-oxa-1,3-butadienes. *Curr. Org. Chem.* **1998**, *2*, 19–62. (g) Singer, M.; Ryan, W. J.; Saha, B.; Martin, B. R.; Razdan, R. K. Potent Cyano and Carboxamido Side-Chain Analogs of 1′,1′-Dimethyl- Δ^8-Tetrahydrocannabinol. *J. Med. Chem.* **1998**, *41*, 4400–4407. (h) Evans, D. A.; Shaugnessy, E. A.; Barnes, D. M. Cationic Bis(oxazoline)Cu(II) Lewis Acid Catalysts. Application to the Asymmetric Synthesis of *ent*- Δ^1-Tetrahydrocannabinol. *Tetrahedron Lett.* **1997**, *38*, 3193–3194.

(6) (a) Kapeller, D. C.; Bräse, S. Towards a Library of Chromene Cannabinoids: A Combinatorial Approach on Solid Supports. *Synlett* **2011**, 161–164. (b) Lesch, B.; Toräng, J.; Nieger, M.; Bräse, S. The Diels-Alder Approach towards Cannabinoids. *Synthesis* **2005**, 1888–1900. (c) Lesch, B.; Toräng, J.; Vanderheiden, S.; Bräse, S. Base-catalyzed Condensation of 2-Hydroxybenzaldehyes with α,β-Unsaturated Aldehydes − Scope and Limitations. *Adv. Synth. Catal.* **2005**, *347*, 555–562.

(7) Merrifield, R. B. Solid Phase Peptide Synthesis. I. The Synthesis of a Tetrapeptide. *J. Am. Chem. Soc.* **1963**, *85*, 2149–2154.

(8) Wang, S.-S. *p*-Alkoxybenzyl Alcohol Resin and *p*-Alkoxybenyloxycarbonylhydrazide Resin for Solid Phase Synthesis of Protected Peptide Fragments. *J. Am. Chem. Soc.* **1973**, *95*, 1328–1333.

(9) Thompson, L. A.; Ellman, J. A. Straightforward and General Method for Coupling Alcohols to Solid Supports. *Tetrahedron Lett.* **1994**, *35*, 9333–9336.

(10) (a) Bräse, S.; Köbberling, J.; Enders, D.; Wang, M.; Lazny, R.; Brandtner, S. Triazenes as Robust and Simple Linker for Amines in Solid-Phase Organic Synthesis. *Tetrahedron Lett.* **1999**, *40*, 2105–2108. (b) Dahmen, S.; Bräse, S. The First Stable Diazonium Ion on Solid Support − Investigations on Stability and Usage as Linker and Scavenger in Solid-Phase Organic Synthesis. *Angew. Chem., Int. Ed.* **2000**, *39*, 3681–3683.

(11) For procedures see Supporting Information.

(12) (a) Review: Ziegert, R. E.; Toräng, J.; Knepper, K.; Bräse, S. Recent Impact of Solid-Phase Synthesis on Medicinally Relevant Benzoannelated Oxygen Heterocycles. *J. Comb. Chem.* **2005**, *7*, 147–169. (b) Oh, S.; Jang, H. J.; Ko, S. K.; Ko, Y.; Park, S. B. Construction of a Polyheterocyclic Benzopyran Library with Diverse Core Skeletons through Diversity-Oriented Synthesis Pathway. *J. Comb. Chem.* **2010**, *12*, 548–558. (c) Nicolaou, K. C.; Pfefferkorn, J. A.; Cao, G.-Q. Selenium-Based Solid-Phase Synthesis of Benzopyrans I: Application to Combinatorial Synthesis of Natural Products. *Angew. Chem., Int. Ed.* **2000**, *39*, 734–739. (d) Nicolaou, K. C.; Cao, G.-Q.; Pfefferkorn, J. A. Selenium-Based Solid-Phase Synthesis of Benzopyrans II: Application to Combinatorial Synthesis of Medicinally Relevant Small Organic Molecules. *Angew. Chem., Int. Ed.* **2000**, *39*, 739–743. (e) Nicolaou, K. C.; Pfefferkorn, J. A.; Roecker, A. J.; Cao, G.-Q.; Barluenga, S.; Mitchell, H. J. Natural Product-like Combinatorial Libraries based on Privileged Structures. I. General Principles and Solid-Phase Synthesis of Benzopyrans. *J. Am. Chem. Soc.* **2000**, *122*, 9939–9948. (f) Hong, B.-C.; Chen, Z.-Y.; Chen, W.-H. Traceless Solid-Phase Synthesis of Heterosteroid Framework. *Org. Lett.* **2000**, *2*, 2647–2649.

(13) Shi, Y.-L.; Shi, M. The synthesis of chromenes, chromanes, coumarins and related heterocycles via tandem reactions of salicylic

aldehydes or salicylic imines with α,β-unsaturated compounds. *Org. Biomol. Chem.* **2007**, *5*, 1499–1504.

(14) (a) Das, B. C.; Mohapatra, S.; Campbell, P. D.; Nayak, S.; Mahalingam, S. M.; Evans, T. Synthesis of function-oriented 2-phenyl-2*H*-chromene derivatives using L-pipecolinic acid and substituted guanidine organocatalysts. *Tetrahedron Lett.* **2010**, *51*, 2567–2570. (b) Ibrahem, I.; Sundén, H.; Rios, R.; Zhao, G.-L.; Córdova, A. One-Pot Pyrrolidine-Catalyzed Synthesis of Benzopyrans, Benzothiopyranes, and Dihydroquinolidines. *Chimia* **2009**, *61*, 219–223.

(15) Satoh, Y.; Stanton, J. L.; Hutchison, A. J.; Libby, A. H.; Kowalski, T. J.; Lee, W. H.; White, D. H.; Kimble, E. F. Substituted chromenes as potent, orally active 5-lipoxygenase inhibitors. *J. Med. Chem.* **1993**, *36*, 3580–3594.

(16) (a) Gérard, E. M. C.; Sahin, H.; Encinas, A.; Bräse, S. Systematic Study of a Solvent-Free Mechanochemically Induced Domino Oxa-Michael-Aldol Reaction in a Ball Mill. *Synlett* **2008**, 2702–2704. (b) Nising, C. F.; Bräse, S. The Oxa-Michael-Reaction: From Recent Developments to Applications in Natural Product Synthesis. *Chem. Soc. Rev.* **2008**, *37*, 1218–1288.

(17) Analogous conditions imply similar amounts of reagents/mL of solvent. The actual amount of reagents compared to starting material is higher in the solid phase approach, which takes lower reactivity into account as well as the necessary amount of solvent for ideal quelling of the resin.

(18) DOMA condensation with **7**{*4*} was not repeated in solution phase because of the low yield in solid phase.

(19) This was the only Wittig salt tried so far, as otherwise the resulting additional stereoisomers would complicate the final separation step.

(20) Minami, T.; Matsumoto, Y.; Nakamura, S.; Koyanagi, S.; Yamaguchi, M. 3-Vinylcoumarins and 3-Vinylchromenes as Dienes. Application to the Synthesis of 3,4-Fused Coumarins and Chromenes. *J. Org. Chem.* **1992**, *57*, 167–173.