A Novel Approach to Monobenzannulated Spiroketals Using Styrenes in the Kulinkovich Reaction

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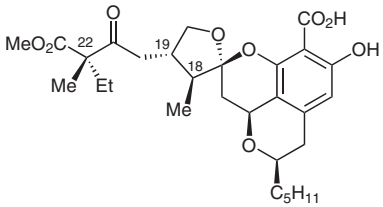
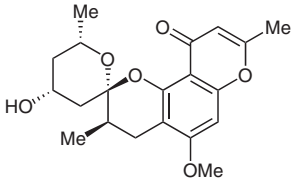
Abstract: The synthesis of a series of 5,6-monobenzannulated spiroketals is reported. The use of various styrenes in a Kulinkovich reaction with an appropriately functionalized aliphatic ester affords cyclopropanol products which under basic conditions underwent ring opening to form ketone precursors to the spiroketals. Deprotection of the hydroxyl groups and subsequent cyclization afforded monobenzannulated spiroketals related to the core structure of berkelic acid.

Key words: Kulinkovich reaction, ring opening, cyclopropanol, spiroketal, berkelic acid

Spiroketals are found in a wide range of natural products that exhibit a variety of biological activities thus rendering them privileged structures.[1,2] An interesting subgroup of aromatic spiroketals include the monobenzannulated spiroketals such as berkelic acid (**1**)[3] and chaetoquadrin A (**2**,[4] Figure 1).



berkelic acid (**1**)



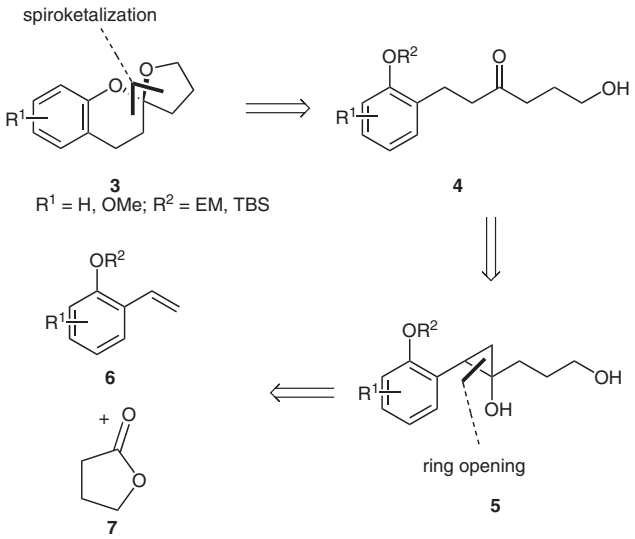
chaetoquadrin A (**2**)

Figure 1 Monobenzannulated spiroketal-containing natural products

Berkelic acid (**1**) consists of a novel aromatic 5,6-spiroketal embedded in a highly substituted tetracyclic framework. Berkelic acid (**1**) was recently isolated from a fungal extremophile, a *Penicillium* species, found in a highly acidic and metal-contaminated abandoned copper mine in Montana, USA.[3] Berkelic acid (**1**) exhibits selective activity towards OVCAR-3, an ovarian cancer cell line. It is also an inhibitor of MMP-3 and caspase-1, providing an attractive target for the development of anticancer agents. Recently, Fürstner et al.[5] reported a synthesis-driven structure revision of berkelic acid reassigning the stereochemistry at C18 and C19. Shortly after, Snider et al.[6] completed the first total synthesis of berkelic acid further confirming the reassignment of stereochemistry at C18 and C19, as well as assigning the stereochemistry at C22. Chaetoquadrin A (**2**), containing an aryl 6,6-spiroketal, was recently isolated from an ascomycete, *Chaetomium quadrangulatum*, and possesses monoamine oxidase inhibitory activity.[4]

Methods for the construction of monobenzannulated spiroketals include use of a hetero-Diels–Alder reaction between an *o*-quinone methide and an *exo*-enol ether,[7] palladium-catalyzed synthesis via a one-pot, multicomponent cascade reaction,[8] and a cross-metathesis–radical cyclization approach, developed in our laboratory.[9]

Recently, our attention has focused on the formation of the tricyclic spiroketal core **3** of berkelic acid. It was envisaged that monobenzannulated 5,6-spiroketals of type **3** could be synthesized via Kulinkovich coupling[10–14] of a substituted styrene **6** and γ-butyrolactone (**7**) followed by selective ring opening of the resulting cyclopropanol **5** and subsequent cyclization (Scheme 1).



Scheme 1 Retrosynthesis of monobenzannulated spiroketals **3**

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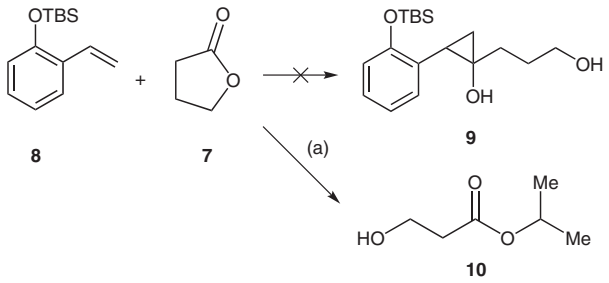
To the best of our knowledge, the use of styrenes in the Kulinkovich reaction is limited to just one example,[14] and the reaction itself has found limited use in natural product synthesis.[15–17] We were therefore attracted to the possible application of the Kulinkovich reaction to the synthesis of monobenzannulated spiroketals related to berkelic acid (**1**).

Initially, the intent was to couple TBS-protected hydroxystyrene **8** with readily available γ-butyrolactone (**7**)[15,18] to afford the diol **9**.

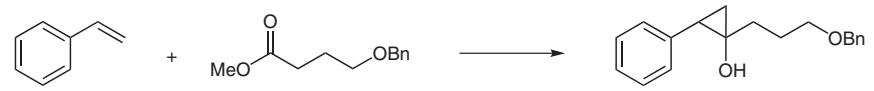


Scheme 2 Reaction of **8** with γ-butyrolactone. *Reagents and conditions:* Ti(O*i*-Pr)$_4$ (3 equiv), *c*-$C_6H_{11}MgCl$ (6 equiv), toluene, r.t., 19 h.

Coupling of **8** and **7** in the presence of cyclohexylmagnesium bromide and Ti(O*i*-Pr)$_4$ in toluene at room temperature failed to give **9**, with isopropopyl ester **10** being the only product formed (Scheme 2). Numerous variations in the solvent, the quantity of Grignard reagent and Ti(O*i*-Pr)$_4$ failed to provide cyclopropanol **9**. This outcome might be attributed to the steric hindrance of the TBS protecting group. Hence, the protecting group was changed to an ethoxymethyl (EM) group. In addition, lactone **7** was substituted by the linear butanoate **12**, and the Kulinkovich reaction was first performed on readily available styrene **11**. Kulinkovich studied the nature of the Grignard reagent in the reaction of styrene with ethyl acetate,[14] establishing that butylmagnesium bromide was the best Grignard reagent for reactions using styrene. Adding butylmagnesium bromide dropwise to a solution of **11**, **12**, and Ti(O*i*-Pr)$_4$ in ethyl acetate afforded cyclopropanol **13** in 26% yield after reflux for 2 hours (Table 1, entry 1). Disappointingly, the reaction mixture also contained a significant amount of isopropyl ester of **12** (36%).

Increasing the amount of Ti(O*i*-Pr)$_4$ and **12** did not afford a better yield (entry 2). The last step in the reaction mechanism is the oxidative addition of the ester to the titanacyclopentane intermediate. Hence, the order of addition of the reagents was changed and **12** was added last to the reaction mixture (entries 3–7). The Grignard reagent was also changed to cyclohexylmagnesium chloride, which has been reported to shift the equilibrium of the ligand exchange to the desired titanacyclopropane.[12b] Thus, cyclohexylmagnesium chloride was added to a solution of Ti(O*i*-Pr)$_4$ in THF at –78 °C over 20 minutes in order to form the titanacyclopropane complex.[19] After addition of **11**, the suspension was stirred for 1 hour, followed by the addition of **12** with subsequent warming to room temperature. Cyclopropanol **13** was only obtained in 16% yield in this case (entry 3). On the other hand, raising the temperature to –50 °C increased the yield to 50% (entry 4). Increasing the amount of Ti(O*i*-Pr)$_4$ and Grignard reagent gave a slightly improved 52% yield (entry 5). Raising the temperature to –35 °C improved the yield further to 59% (entry 6) but warming further to –20 °C decreased the yield of cyclopropanol **13** (entry 7).

Table 1 Optimization for Kulinkovich Coupling of **11** with **12**

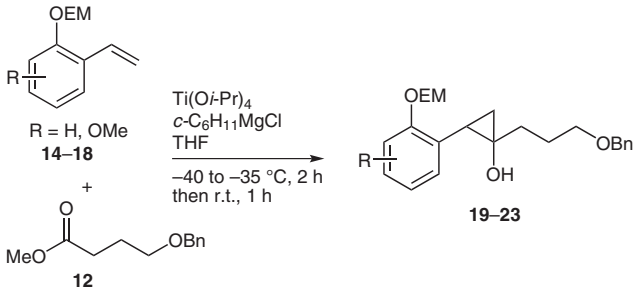


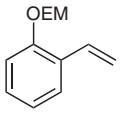
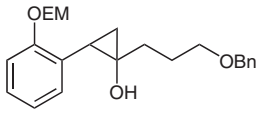
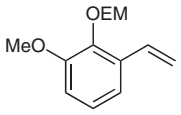
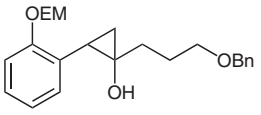
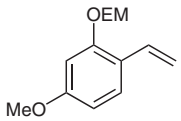
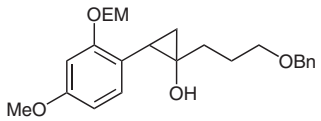
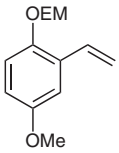
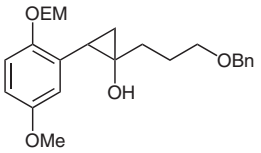
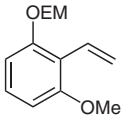
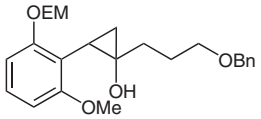
11 **12** **13**

Entry	Ti(O*i*-Pr)$_4$ (equiv)	**11** (equiv)	**12** (equiv)	Grignard (equiv)	Solvent	Temp	Time (h)	Yield of **13** (%)[c]
1[a]	0.1	2	1	*n*-BuMgBr (2.5)	Et_2O	reflux	0.75	26
2[a]	0.5	1	2	*n*-BuMgBr (2.5)	Et_2O	reflux	2	21
3[b]	1	1	1	*c*-$C_6H_{11}MgCl$ (3)	THF	–78 °C then r.t.	18	16
4[b]	1	1	1	*c*-$C_6H_{11}MgCl$ (3)	THF	–50 °C then r.t.	3	50
5[b]	3	1	1	*c*-$C_6H_{11}MgCl$ (9)	THF	–50 °C then r.t.	3	52
6[b]	3	1	1	*c*-$C_6H_{11}MgCl$ (9)	THF	–35 °C then r.t.	1	59
7[b]	3	1	1	*c*-$C_6H_{11}MgCl$ (9)	THF	–20 °C then r.t.	2	18

[a] Addition sequence: Ti(O*i*-Pr)$_4$, **11**, **12**, then *n*-BuMgBr.
[b] Addition sequence: Ti(O*i*-Pr)$_4$, *c*-$C_6H_{11}MgBr$, **11**, then **12**.
[c] Yield of isopropyl ester of **12**: entry 1: 36%; entries 2–7: trace.

Table 2 Kulinkovich Reaction of Olefins **14–18** with **12**

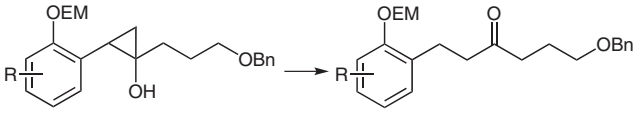


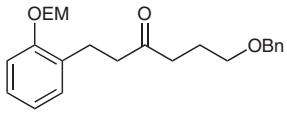
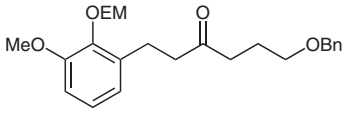
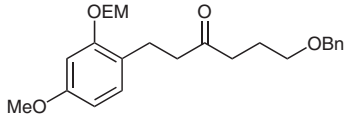
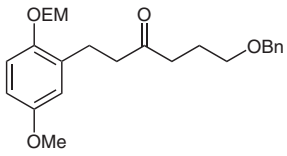
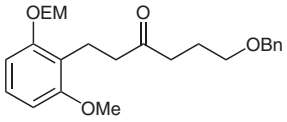
Olefin	Product	Yield (%)
 **14**	 **19**	42
 **15**	 **20**	30
 **16**	 **21**	33
 **17**	 **22**	30
 **18**	 **23**	25

Having optimized the reaction conditions using styrene, attention next turned to the use of olefins **14–18**. Olefins **14** and **15** were synthesized from salicylaldehyde and *o*-vanillin, respectively, in two steps by Wittig olefination[20] followed by protection as an ethoxymethyl ether.[21] Olefins **16–18** were obtained from their corresponding dimethoxybenzaldehydes by monodeprotection using BCl_3,[22] Wittig olefination and protection as an ethoxymethyl ether. With the appropriate olefins in hand, the Kulinkovich reaction was carried out using the conditions optimized for styrene. All of the Kulinkovich reactions afforded complex mixtures from which the desired cyclopropanols **19–23** were isolated in low to moderate yields (Table 2).

Having synthesized the required cyclopropanols **19–23**, attention next turned to their ring opening to the corresponding ketones **24–28**. Use of $Fe(NO_3)_3$ and Bu_3SnH in DMF[15] did not effect cleavage of cyclopropanol **19** to ketone **24**, prompting investigation of alternative reagents.[23] Use of NaOH in dioxane proceeded with 100% selectivity for C_1–C_2 cleavage. The optimum conditions involved using 0.2 N NaOH–dioxane (2:1) at reflux for three days. Attempts to improve the reaction using microwave irradiation afforded the desired ketone **24** in the same yield after 15 minutes at 80 °C. Thus, these latter conditions were used to effect the formation of ketones **25–28** from cyclopropanols **20–23** (Table 3).

Table 3 Ring-Opening Reactions of Cyclopropanols **19–23**



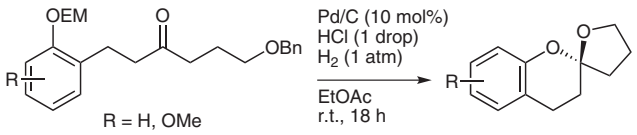
Cyclopropanol	Product	Yield (%)
19	 **24**	48[a]
20	 **25**	50[a]
21[21]	 **26**	50[b]
22	 **27**	52[a]
23	 **28**	42[b]

[a] Reaction conditions: 0.2 N NaOH–dioxane (2:1), reflux, 3 d.
[b] Reaction conditions: 0.2 N NaOH–dioxane (2:1), MW, 200 W, 80 °C, 15 min.

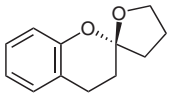
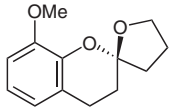
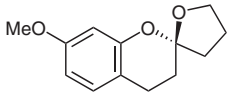
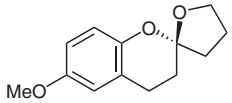
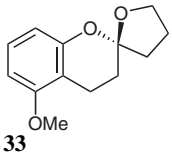
With ketones **24–28** in hand, deprotection and subsequent cyclization to the desired spiroketals was finally examined.[25]

Hydrogenolysis of ketones **24** and **26**[26] over Pd/C in ethyl acetate containing 10% HCl[24] afforded spiroketals **29** and **31** in 66% and 38% yield, respectively. Pearlman's catalyst was used to form spiroketals **30**, **32**, and **33** from their corresponding ketones in 35%, 37%, and 58% yield, respectively (Table 4).

Table 4 Acid-Catalyzed Spirocyclization of Ketones **24–28**



24–28 **29–33**

Ketone	Product	Catalyst	Yield (%)
24	 **29**	Pd/C	66
25	 **30**	$Pd(OH)_2$	35
26	 **31**	Pd/C	38
27	 **32**	$Pd(OH)_2$	37
28	 **33**	$Pd(OH)_2$	58

In conclusion, the synthesis of a series of monobenzannulated 5,6-spiroketals, analogous to the spiroketal unit of berkelic acid (**1**), has been achieved using a novel Kulinkovich cyclopropanol–ring opening strategy involving union of a styrene with an aliphatic ester.

Acknowledgment

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References and Notes

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(25) **General Procedure – Kulinkovich Reaction**
A solution of $Ti(O\textit{i}\text{-}Pr)_4$ (2.16 mmol) in THF (5 mL) was cooled to an internal temperature of –40 °C. *c*-$C_6H_{11}MgCl$ (6.49 mmol) was added at such a rate that the internal temperature did not exceed –35 °C. Styrene (0.72 mmol) was added and the orange-brown suspension stirred for 2 h at –35 °C. Ester (0.72 mmol) was added and the suspension warmed to r.t. whereupon a brown color developed. After stirring for 1 h, the suspension was diluted with EtOAc (75 mL) and poured into sat. NH_4Cl solution (75 mL). The emulsion was stirred vigorously for 30 min then filtered through a pad of Celite®. The aqueous layer was extracted with EtOAc (3 × 75 mL), then the combined organic phases were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The crude product was purified by flash chromatography (hexane–EtOAc, 2:1) to afford the cyclopropanol.
1-[3-(Benzyloxy)propyl]-2-[2-(ethoxymethoxy)-4-methoxyphenyl]cyclopropanol (21)
Yellow oil. R_f = 0.23 (hexane–EtOAc, 2:1). IR (film): ν = 3440, 2928, 1711, 1610, 1505, 1453, 1360, 1279, 1254, 1199, 1156, 1100, 1075, 996, 842, 736, 689 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (dd, *J* = 7.3, 5.7 Hz, 1 H, H-2), 1.12–1.29 (m, 4 H, CH_3, H-3), 1.56 (dd, *J* = 14.4, 7.4 Hz, 2 H, H-1′), 1.70 (quin, *J* = 6.3 Hz, 2 H, H-2′), 2.30 (dd, *J* = 9.9,

7.3 Hz, 1 H, H-3), 3.48 (t, *J* = 5.8 Hz, 2 H, H-3′), 3.74 (q, *J* = 7.1 Hz, 2 H, OC*H*$_2$CH$_3$), 3.78 (s, 3 H, OMe), 4.47 (s, 2 H, OCH$_2$Ph), 5.25 (q, *J* = 6.3 Hz, 2 H, OCH$_2$O), 6.45 (dd, *J* = 8.4, 2.5 Hz, 1 H, H-5′), 6.73 (d, *J* = 2.5 Hz, 1 H, H-3′), 6.79 (d, *J* = 8.4 Hz, 1 H, H-6′), 7.27–7.34 (m, 5 H, OBn). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1 (CH_3), 17.1 (CH_2, C-3), 25.9 (CH_2, C-2′), 26.1 (CH, C-2), 31.4 (CH_2, C-1′), 55.3 (CH_3, OMe), 64.2 (q, C-1), 70.7 (CH_2, O*C*H$_2$CH$_3$), 72.9 (CH_2, OCH$_2$Ph), 93.4 (CH_2, OCH$_2$O), 101.4 (CH, C-4″), 105.6 (CH, C-5″), 127.6 (CH, C-6″), 127.7 (CH, C-2‴, C-6‴), 128.2 (CH, C-4‴), 128.4 (CH, C-3‴, C-5‴), 148.7 (q, C-1″, C-1‴), 159.0 (q, C-2″, C-3″). MS (EI, 70eV): *m/z* (%) = 247 (16), 409 (100) [M$^+$ + Na], 793 (2 M$^+$ + Na]. HRMS (EI): *m/z* [M$^+$ + Na] calcd for $C_{23}H_{30}NaO_5$: 409.1991; found: 409.1985.

(26) **General Procedure – Ring Opening of Cyclopropanols**

Cyclopropanol (0.34 mmol) was added to dioxane (3 mL) and 0.2 N NaOH solution (6 mL). The reaction was stirred at reflux for 3 d, then neutralized to pH 7 with 2 M HCl. The aqueous layer was extracted with Et_2O (5 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The crude product was purified by flash chromatography (hexane–EtOAc, 4:1) to afford the ketone.

6-(Benzyloxy)-1-[2-(ethoxymethoxy)-4-methoxyphenyl]hexan-3-one (26)

Yellow oil. R_f = 0.38 (hexane–EtOAc, 4:1). IR (film): ν = 2927, 1712, 1610, 1587, 1506, 1444, 1361, 1284, 1256, 1199, 1154, 1100, 1077, 997, 842, 737, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3 H, OCH$_2$C*H*$_3$), 1.88 (quin, *J* = 6.7 Hz, 2 H, H-5), 2.50 (t, *J* = 7.3 Hz, 2 H, H-4), 2.66 (t, $J_{A,B}$ = 7.7 Hz, 2 H, H-2), 2.81 (t, $J_{A,B}$ = 7.4 Hz, 2 H, H-1), 3.46 (t, *J* = 6.4 Hz, 2 H, H-6), 3.71 (q, *J* = 7.0 Hz, 2 H, OC*H*$_2$CH$_3$), 3.77 (s, 3 H, OMe), 4.47 (s, 2 H, OCH$_2$Ph), 5.22 (s, 2 H, OCH$_2$O), 6.46 (dd, *J* = 8.3, 2.6 Hz, 1 H, H-5′), 6.70 (d, *J* = 2.5 Hz, 1 H, H-3′), 7.01 (d, *J* = 8.0 Hz, 1 H, H-6′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.1 (CH_3), 23.8 (CH_2, C-5), 24.3 (CH_2, C-1), 39.4 (CH_2, C-4), 43.2 (CH_2, C-2), 55.3 (CH_3, OMe), 64.3 (CH_2, O*C*H$_2$CH$_3$), 69.4 (CH_2, C-6), 72.8 (CH_2, OCH$_2$Ph), 93.1 (CH_2, OCH$_2$O), 101.4 (CH, C-3′), 105.8 (CH, C-5′), 127.5 (CH, C-4″), 127.6 (CH, 2″, C-6), 128.4 (CH, C-3″, C-5″), 130.1 (q, C-1′), 130.2 (CH, C-6′), 138.7.9 (q, C-1″), 156.0 (q, C-2′), 159.2 (q, C-4′), 210.8 (q, C-3). MS (EI, 70eV): *m/z* (%) = 97 (19), 151 (55), 177 (82), 207 (27), 235 (67), 253 (19), 275 (17), 311 (46), 341 (31), 385 (5) [M$^+$], 409 (100) [M$^+$ + Na]. HRMS (EI): *m/z* [M$^+$ + Na] calcd for $C_{23}H_{30}NaO_5$: 409.1991; found: 409.1985.