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Lessons learned while traversing the welwitindolinone alkaloids obstacle course☆

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ABSTRACT

We recount several unexpected results observed in the course of our work toward the synthesis of welwitindolinone alkaloids. The surprising results provide an opportunity to refine one's understanding of the interplay between chemical structure and reactivity.

1. Introduction

In the course of complex natural product synthesis, seemingly straightforward steps often yield unexpected results. Indeed, it is the exception rather than the norm that a multi-step synthesis proceeds precisely as planned; and it is this unpredictability that makes the field not only challenging, but also interesting. The unplanned results provide an opportunity to refine one's understanding of the interplay between chemical structure and reactivity. In our ongoing efforts[1] toward the synthesis of the welwitindolinone alkaloids (**1**–**3**, Fig. 1),[2–4] we have encountered more than a few hurdles along the way, and these have introduced new twists and turns in our synthetic strategy and have also provided some chemical surprises. We recount below several of the planned transformations and discuss the unforeseen outcomes. While some of the unexpected results have yet to be understood fully, others provide fresh insights on chemical reactivity.

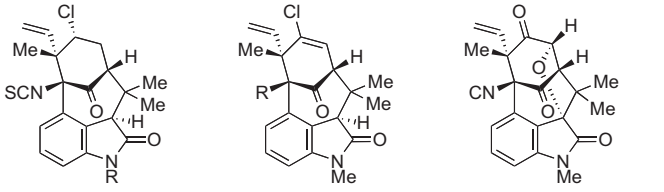

Fig. 1. Representative welwitindolinone alkaloids.

2. Results and Discussion

2.1. Regioselectivity and C- vs. O- selectivity

We recently reported a concise synthesis of the welwitindolinone core via an oxidative arylation approach, which enabled the synthesis of diketone **5** from ketoester **4**.[1c] The presence of the ester functionality was expected, whether through chelation or an electronic inductive effect, to enable regioselective functionalization of the desired α-carbon of the C13-ketone. Among the transformations that were examined to achieve this goal was a sequence involving a Vilsmeier–Haack reaction followed by deconjugative methylation (Scheme 1).[5] The caged architecture of **6** renders only the convex face accessible to electrophiles, thus the methylation event was expected to occur with complete facial selectivity. Wittig methylenation of the tertiary aldehyde in **8** would then complete the C12 quaternary center.

To put the plan into action, dione **5** was subjected to standard Vilsmeier–Haack conditions ($POCl_3$, DMF, heat), and, while it produced a β-chloro-aldehyde product, it was solely the undesired regioisomer, **10** (Scheme 2). Varying the reaction conditions did not invert the inherent regioselectivity of this reaction.

☆ This paper is submitted in celebration of the 90th birthday of Professor Gilbert Stork, whose unequaled creativity and boundless generosity has inspired generations of chemists, including the authors of the present publication.

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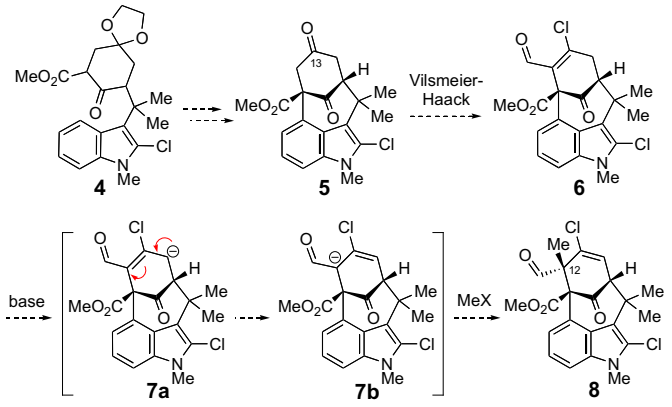
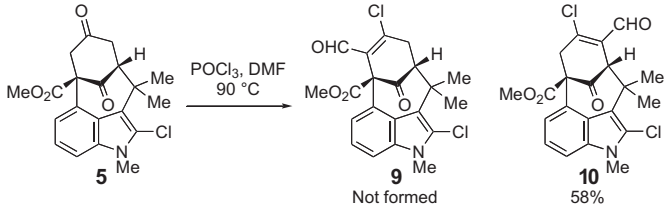
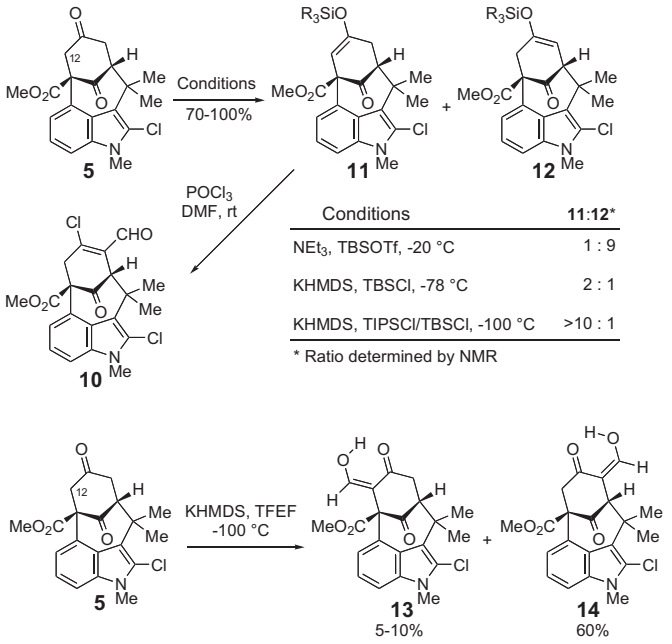


Scheme 1. Vilsmeier–Haack deconjugative methylation approach.



Scheme 2. Vilsmeier–Haack chloroformylation of dione **5**.



Scheme 3. Attempts to functionalize the C12-position of dione **5**.

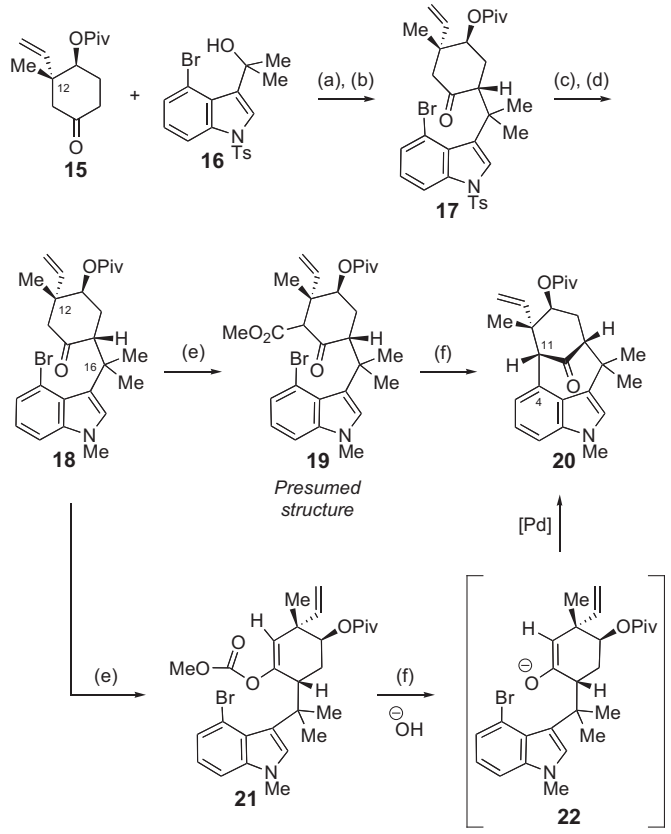
The regioselectivity of chloroformylation appeared inconsistent with the anticipated reactivity of the ketone, particularly with respect to the effect of the β-carboxylate group. To determine the inherent deprotonation selectivity, we investigated the conversion of the ketone to the corresponding silyl enol ether. Should that take place in the desired fashion, then that selectivity could be parlayed into the desired Vilsmeier–Haack reaction. To our surprise, silyl enol ether formation under soft-enolization conditions gave predominantly the undesired product (**12**, Scheme 3). The selectivity was reversed, however, under kinetic conditions. Indeed, deprotonation of dione **5** with KHMDS and quenching with an appropriate silyl chloride at −100 °C afforded the desired enol ether **11** with high regiocontrol. The presence of acidic by-products in the Vilsmeier–Haack reaction prompted us to favor bulky silyl groups like TBS and TIPS, which display higher stability to acidic conditions over the smaller and more labile TMS or TES groups. With the desired regioisomer of silyl enol ether (**11**) at hand we were poised to test the key Vilsmeier–Haack reaction. Treatment of **11** with the Vilsmeier–Haack reagent, generated in situ, once again yielded only the undesired regioisomer of the β-chloro-aldehyde (**10**). Investigation of the reaction revealed that the silyl enol ether (**11**) was undergoing isomerization under the reaction conditions to its regioisomer (**12**), which was responsible for the observed product (**10**). As the double bond isomerization is expected to be promoted by acid, the reaction was performed in the presence of various amine bases. Under these conditions, however, there was no reaction, and the starting silyl enol ether (**11**) was recovered in all cases.

In a closely related strategy for installing the functionality at the neopentyl carbon (C12), we had hoped to capitalize on the successful kinetic deprotonation of dione **5** and functionalize the α-carbon. With that objective, the kinetic enolate was treated with Zayia's reagent[6] to afford the desired ketoaldehyde (**13**), albeit as the minor constituent of the reaction mixture. Disappointingly, this compound resisted our attempts at C-methylation. The *O*-methylated product was obtained as the predominant product, even under conditions known to favor C-methylation. The result highlighted for us the limitations that exist in the available methodology for a simple methylation reaction. The issue of C- vs. O-selectivity is one that we also confronted in a different route, as described below.

3. Unexpected Pd-catalyzed arylation product

The inability to install the C12 quaternary center after assembling the core skeleton forced us to alter the strategy and perform the key C4–C11 bond forming step on a substrate that already had in place the requisite functionalities. To that end, we choose cyclohexanone **15**,[7] having the methyl and vinyl groups at C12, and converted it to compound **18** via a short sequence of steps (Scheme 4).[8] With the indole-containing fragment attached, ketone **18** was treated with LDA followed by Mander's reagent to deliver the expected carbomethoxylated product **19** (shown in the ketoester form), which was ready for the key Pd-enolate arylation step. Subjection of β-ketoester **19** to the palladium-mediated arylative-cyclization conditions (KO^{t}Bu, palladium(II) acetate, and P^{t}Bu$_3$)[1a] afforded a tetracyclic product in modest yield. Curiously, the isolated product (**20**) lacked the C11 ester functionality, a surprising omission that was initially attributed to a hydrolytic-decarboxylation, a side reaction that was presumed to follow the palladium cyclization event. While plausible at first glance, this result was inconsistent with our earlier experiences using a model system, wherein a related ester was found to be highly resistant to basic hydrolysis.[1a] Moreover, the geometric constraints enforced by the bridged skeleton preclude the required stereoelectronic positioning of the carboxylate to the ketone. A careful examination of the overall reaction and the starting material provided the answer: there was an error in the structure assigned to the cyclization precursor (**19**). Acylation of the enolate of **18** with Mander's reagent had delivered not the expected ketoester **19**, but the enol carbonate **21**. Evidently, the congested surroundings, specifically the quaternary centers at C12- and C16-position, disfavor reaction of the electrophile at the carbon, allowing reaction only at the oxygen. After confirming the structure of the acylation product, it was then possible to provide a reasonable explanation for the formation of the decarboxylated product (**20**). Given the susceptibility of the enol carbonate to nucleophiles, it is likely that adventitious water, whether in the solvent or in the reagents, cleaves the enol carbonate **21**. The resulting enolate (**22**) then undergoes a palladium-

catalyzed intramolecular enolate arylation to provide tetracycle **20**. Indeed, when the same reaction was performed under rigorously anhydrous conditions, none of the cyclized product (**20**) was observed. Various conditions and reagents were tried in order to functionalize the C11-position with a withdrawing group, but to no avail.[9] The above difficulties forced us once again to modify the route and examine the possibility of installing the needed C11 electron-withdrawing group *before* coupling with the indole fragment.



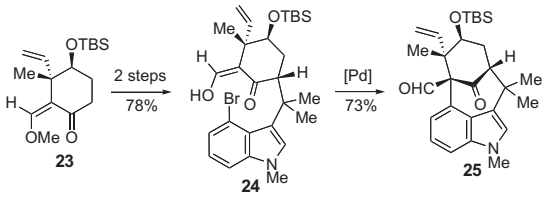
(a) **15**, LDA, TMSCl; (b) $SnCl_4$, -78 °C, 48%, 2 steps;
(c) KOH, EtOH; (d) MeI, TBAOH, 83%, 2 steps;
(e) LDA, HMPA, MeOC(O)CN, 96%; (f) $Pd(OAc)_2$, P*t*Bu_3, KO*t*Bu, 70 °C, 34%.

Scheme 4. Formation of the decarboxylated welwitindolinone skeleton.

To circumvent the difficulties encountered with installation of the C11-withdrawing group, we decided to start with a more functionalized cyclohexanone fragment (**23**, Scheme 5). To our delight, this strategy proved successful and provided an efficient route to the fully functionalized welwitindolinone core (**25**), which ultimately culminated in the synthesis of *N*-methyl welwitindolinone D isonitrile (**3**).[1b] Tetracycle **25** was also expected to lay the path to several other welwitindolinones, especially toward welwitindolinone B (**1**), which required deoxygentative chlorination, indole oxidation, and conversion of the aldehyde to an isothiocyanate moiety.

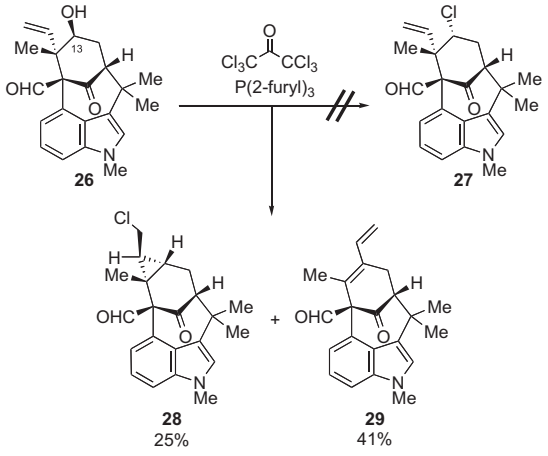
4. Chlorination and chloroselenation surprises

In order to progress to welwitindolinone B (**1**), the C13 hydroxyl in **26** (Scheme 6) had to be transformed to the chloride, with inversion of configuration. Unfortunately, this simple transformation proved an insurmountable task and, even after considerable experimentation, we were unable to install the requisite halide at the C13-position of alcohol **26**. Interestingly, when alcohol **26** was



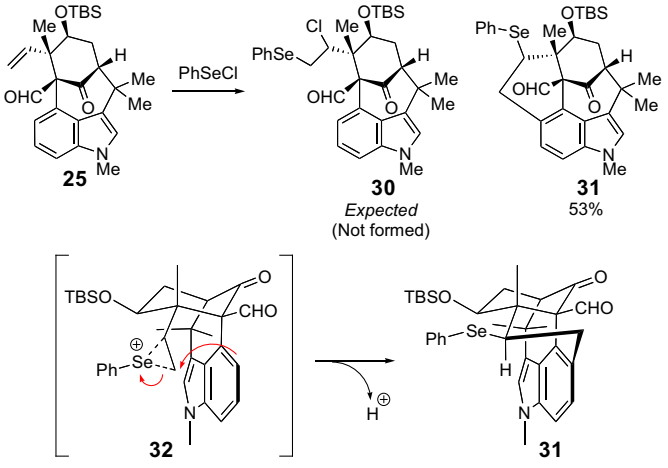
Scheme 5. Successful synthesis of the functionalized welwitindolinone core.

exposed to tri(2-furyl)phosphine and hexachloroacetone, it produced none of the desired chloride **27**, but gave instead a fascinating rearrangement giving rise to cyclopropane **28** and diene **29**.[10] Interaction by the neighboring vinyl group evidently diverts the reaction from its normal course and produces compounds **28** and **29**.



Scheme 6. Unexpected rearrangement during deoxygenative chlorination.[10]

Another unexpected reaction was observed while searching for ways to protect the offending vinyl group, and thereby circumvent the homoallylic rearrangement. Attempted chloroselenation of TBS ether **25** with phenylselenium chloride[11a,b] or *N*-(phenylseleno) phthalimide (NPSP)[11c] gave pentacyclic selenide **31** rather than the expected addition product (**30**, Scheme 7). This anomalous result is consistent with the formation of an episelenonium ion (**32**) followed by an intramolecular Friedel–Crafts type reaction instead of

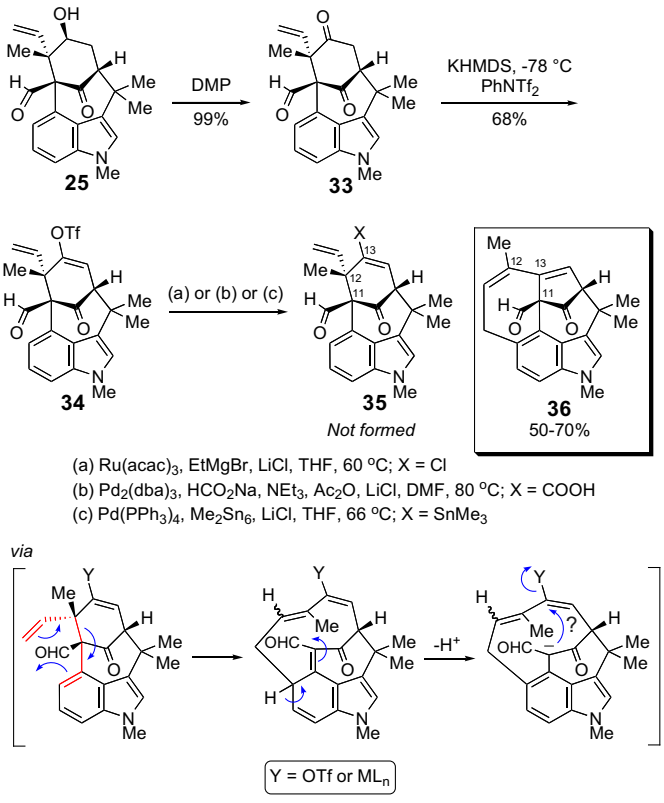


Scheme 7. Unanticipated intramolecular reaction.

the expected trapping by the halide counter ion. The result shows that the alkene is locked in close proximity to the indole-carbocycle. Significantly, the constraints of the system and the stereoelectronic requirements are such that the Friedel–Crafts reaction takes place at the primary carbon.

5. Cross-coupling metamorphosis

The final and most remarkable result that we wish to discuss is a transformation that was encountered during our attempts to synthesize welwitindolinone C (**2**). The identifying feature of this natural product is the alkenyl chloride, a functional group that was expected to be available through the C13-ketone (**33**, Scheme 8), either directly or by way of the *gem*-dichloride. Several methods have been reported in the literature to effect this interconversion on ketones (e.g., WCl_6,[12] PCl_5,[13] $MeSO_3H/AcCl$[14]) or their derivatives.[15] Unfortunately, with a complex substrate such as ketoaldehyde **33** none of these conditions proved successful, and either no reaction or extensive decomposition of the starting material was observed. A less direct route to the alkenyl chloride is through a transition-metal catalyzed functionalization of the corresponding enol triflate, for example, via the alkenyl stannane.[16] In that regard, a recent communication by Hayashi and co-workers disclosed a ruthenium catalyzed transformation of enol triflates to alkenyl halides.[17] A similar conversion, but promoted by a palladium catalyst, was reported by the Buchwald group shortly thereafter.[18] In order to realize these opportunities we set forth to prepare the required alkenyl triflate. The reaction of the dione **33** with KHMDS in THF followed by addition of *N*-phenyl triflimide provided enol triflate **34** in 68% yield (Scheme 8). Upon subjection of **34** to Hayashi's conditions, the starting material was transformed cleanly and in good yield into a new product. This substance was found, however, to not be the desired alkenyl chloride (**35**, X=Cl). Even a cursory examination of its proton NMR indicated that the skeleton of the product was different from that of the starting material. Extensive spectroscopic analysis, particularly HMBC, enabled the structural assignment of the product to be the rearranged compound **36**. Compelling support for the assigned structure was later obtained via X-ray crystallographic analysis (Fig. 2). The same product was also obtained under palladium-catalyzed protocols.[19] The dramatic reorganization of the carbon skeleton which is believed to arise from a Cope rearrangement[20] between the vinyl group and the benzo-portion of indole, followed by C–C bond formation between the nucleophilic carbon (C11) of α-formylketone and the enol triflate carbon (C13).



Scheme 8. Attempts to synthesize the alkenyl chloride.

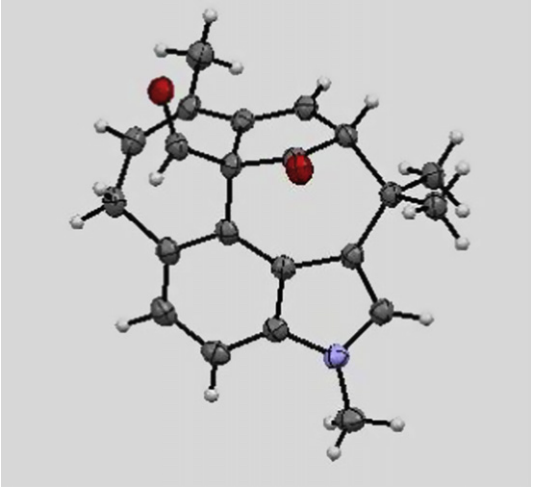
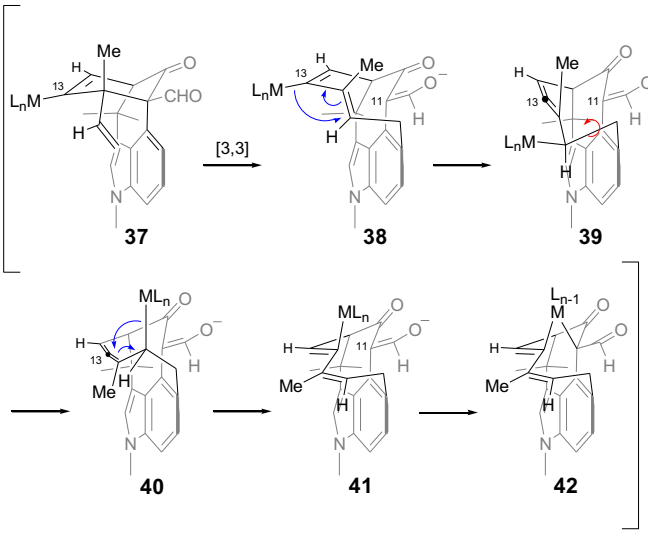


Fig. 2. ORTEP image of **36**.

The mechanistic underpinnings for the above transformation are interesting and informative for several reasons. First, the suggested [3,3]-sigmatropic rearrangement is an 'aromatic Cope' rearrangement, of which there are relatively few examples.[21,22] The loss of aromatic stabilization in the intermediate makes these rearrangements unfavorable unless driven by external factors, namely relief of ring strain, such as that of cyclopropane.[20] The present example is especially noteworthy as the rearrangement takes place at just 60–80 °C. Second, Cope rearrangements typically give *E*- or *Z*-alkenes selectively, depending on whether the reaction is going through a chair or boat transition state. Third, it is unlikely that the enolate that forms after the rearrangement and proton loss can be alkenylated, since the enol triflate is incorrectly oriented for bond formation (**38**). It has *E* rather than the *Z*-geometry required for the intramolecular alkenylation reaction. The alkene geometry must somehow be inverted to enable cyclization. Finally, it is unclear what role if any the metal plays in the [3,3]-rearrangement. With these considerations in mind, we propose the following rationale to explain the overall transformation (Scheme 9).[23] Molecular models show, and the reactivity noted above for chloroselenation confirm, that the [4.3.1]-bridged bicyclic framework is strained—even more so with the enol triflate—and positions the vinyl group in close proximity to the aromatic ring. These strain and topological factors are expected to facilitate the Cope rearrangement. With regard to the *E*/*Z*-geometry of the product, the rigidity of the compound appears to favor the boat transition state over the chair form, such that the methyl-substituted alkene is expected to have *E*-geometry, opposite to what is observed in the final product. The resulting 10-membered ring intermediate with the alkenyl-Ru (or Pd) can undergo a stereospecific η^1 to $\eta^{1'}$ rearrangement, through an alkylidene-π-allyl intermediate, to produce the allenic intermediate **39**.[24] Some of the strain in **39** is relieved through a conformational change, which



Scheme 9. Plausible mechanism for the unusual rearrangement.[23]

gives rise to **40**. A second η^1 to $\eta^{1'}$ rearrangement reforms the diene to yield **41**. The net effect of the two rearrangements is to convert the *E*,*E*-diene (**38**) to the *Z*,*Z*-diene (**41**), having the alkenyl metal bond correctly oriented to enable the intramolecular alkenylation of the stabilized enolate via **42** to deliver pentacycle **36**. It is worth noting that **34** is slowly consumed at 60 °C even in the absence of a catalyst, but gives rise to a mixture of products. Further studies on this fascinating rearrangement are currently underway, details of which will be reported in due course.

The collection of unexpected results presented here serves to affirm what every synthetic organic chemist knows all too well: seemingly small perturbations in the structure of a molecule can significant alter its reactivity.[25] The improved understanding of reactivity gained through this process has been enlightening and is expected to help us define a successful path to several members of the welwitindolinone family.

6. Experimental

6.1. General

Unless stated otherwise, reactions were performed in flame or oven-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents (distilled or passed over a column of activated alumina). Commercially available chemicals were used as received, unless otherwise stated. Ambient temperature refers to 22–26 °C. Higher than ambient reaction temperatures were controlled by IKAmag temperature modulators while for lower temperatures ice (0 °C), ^{i}PrOH/dry ice (−78 °C), and Et_2O/liq N_2 (−100 °C) baths were used. All reactions were monitored by thin-layer chromatography (TLC), which were performed using pre-coated Whatman K6F silica gel (250 μm, 60 Å) plates and Dynamic Adsorbents silica gel (250 μm, 60 Å) plates with F-254 indicator and visualized by UV fluorescence quenching, ceric ammonium molybdate, anisaldehyde, or potassium permanganate staining. Preparative-TLC was performed using Whatman Partisil PK6F pre-coated 60 Å silica gel plates (500 μm) with fluorescent indicator. Zeochem ZEOprep Flash ECO 40-63 Academic Grade silica gel was used for column chromatography. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DRX-400, DRX-500 and DMX-500 and are reported relative to Me_4Si (δ 0.0), unless otherwise stated. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (integration, multiplicity, coupling constant in hertz). Infrared spectra were recorded on Nicolet 6700 FT-IR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded at the Old Dominion University, Norfolk, and Hunter College, New York.

6.2. Chloro-aldehyde 10

A solution of dione **5**[1c] (15.0 mg, 0.04 mmol) in chloroform (0.3 mL) was cooled to 0 °C and DMF (25.0 μL) was added. $POCl_3$ (13.0 μL) was added slowly to the reaction mixture. After 5 min, the reaction mixture was placed in a 90 °C oil bath. After 6 h, the dark red reaction mixture cooled to ambient temperature and was quenched with 2 mL of 0.5 N HCl. The biphasic mixture was extracted with ether (3×5 mL). The combined organic layer was washed with water (3×5 mL), brine (10 mL), and dried (MgSO4). The crude product was purified by preparatory-TLC (plate size: 10×10 cm) with 4:1 hexanes/EtOAc as the eluent to obtain 9.8 mg (58%) of chloro-aldehyde **10**. IR (neat film, NaCl) 2951, 1740, 1716, 1691, 1607, 1476, 1452, 1417, 1371, 1342, 1261, 1200, 1092, 1054, 1037, 968, 910, 734 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 10.00 (1H, s), 7.28–7.23 (2H, m), 6.75 (1H, d, *J*=6.9 Hz), 3.95 (1H, dd, *J*=18.8, 1.8 Hz), 3.84 (1H, d, *J*=1.8 Hz), 3.80 (3H, s), 3.73 (3H, s), 3.23 (1H, d, *J*=18.8 Hz), 1.77 (3H, s), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$) δ 202.7, 191.0, 171.3, 169.1, 144.1, 135.9, 133.8, 128.9, 124.0, 122.5, 119.3, 113.9, 108.6, 67.8, 61.8, 53.0, 52.5, 38.7, 31.9, 31.2, 30.0. HRMS *m*/*z* calcd for $C_{21}H_{19}Cl_2NO_4Na^+$ $[M+Na]^+$: 442.0583, found 442.0582.

6.3. Silyl enol ether 11

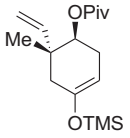
A solution of dione **5** (100 mg, 0.27 mmol) in 2.0 mL THF was cooled to −100 °C. KHMDS (1.33 mL, 0.5 M solution in toluene, 0.67 mmol) was added and the reaction mixture was stirred for 40 min. TBSCl (81.4 mg, 0.54 mmol) in 0.4 mL THF was added and the reaction mixture was allowed to warm up to −10 °C over a period of 1 h. The reaction was quenched with 2 mL of aqueous saturated solution of $NaHCO_3$ and extracted with 1:1 hexanes/ether mixture. Combined organic extracts were washed with water, brine and dried ($MgSO_4$). The crude material was purified via column chromatography (4:1 hexanes/EtOAc) to afford 133.1 mg (~100%) and used immediately afterward for the next step. The corresponding TIPS ether was prepared analogously. ^{1}H NMR of the TBS ether (desired regioisomer, $CDCl_3$) δ 7.18–7.13 (2H, m), 6.62 (1H, dd, *J*=6.7, 1.7 Hz), 5.74 (1H, s), 3.72 (3H, s), 3.71 (3H, s), 2.83 (1H, ddd, *J*=16.9, 7.0, 2.8 Hz), 2.74 (1H, dd, *J*=9.0, 7.0 Hz), 2.34 (1H, ddd, *J*=16.9, 9.0, 1.4 Hz), 1.65 (3H, s), 1.47 (3H, s), 0.84 (9H, s), 0.13 (3H, s), 0.04 (3H, s). ^{1}H NMR of the TIPS ether (desired regioisomer, $CDCl_3$) δ 7.16–7.11 (2H, m), 6.60 (1H, dd, *J*=6.6, 1.7 Hz), 5.74 (1H, s), 3.71 (3H, s), 3.70 (3H, s), 2.86 (1H, ddd, *J*=17.0, 7.2, 2.8 Hz), 2.74 (1H, dd, *J*=9.1, 7.2 Hz), 2.39 (1H, dd, *J*=17.0, 9.1 Hz), 1.66 (3H, s), 1.47 (3H, s), 1.13 (3H, sept, *J*=7.5 Hz), 0.99 (9H, d, *J*=7.4 Hz), 0.94 (9H, d, *J*=7.4 Hz).

6.4. Vinylogous acid 14

A solution of dione **5** (33.0 mg, 0.088 mmol) in THF (0.66 mL) was cooled to −100 °C. KHMDS (0.5 M in toluene, 1.06 mL, 0.53 mmol) was added and the reaction mixture was stirred at −100 °C for 45 min. Neat TFEF (52.0 μL, 0.53 mmol) was added rapidly and the reaction mixture was allowed to warm to 10 °C over 3 h. The reaction was quenched with 0.1 N HCl (2 mL) and was extracted with EtOAc (3×5 mL). The pH of the aqueous layer should be <6 for complete extraction of the products into the organic layer. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude material was purified via preparatory-TLC (plate size 10 cm×20 cm, eluent 4:1 hexanes/EtOAc) to afford acid **14** as a white solid (21.2 mg, 60%) and

~2 mg of **13** (~5%). Data for **14**: IR (neat film, NaCl) 2951, 2917, 1740, 1713, 1638, 1575, 1476, 1451, 1435, 1417, 1370, 1339, 1276, 1250, 1221, 1155, 1082, 1055, 1037, 744 cm^{-1}. ^1H NMR ($CDCl_3$) δ 14.93 (1H, d, J=4.7 Hz), 8.69 (1H, d, J=4.7 Hz), 7.25–7.18 (2H, m), 6.73 (1H, d, J=7.1 Hz), 3.80 (3H, s), 3.72 (3H, s), 3.66 (1H, d, J=18.3 Hz), 3.53 (1H, s), 3.16 (1H, d, J=18.3 Hz), 1.93 (3H, s), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$) δ 204.1, 184.9, 183.8, 171.5, 136.0, 128.0, 124.4, 122.5, 120.3, 119.4, 113.9, 109.6, 108.6, 65.9, 61.6, 52.9, 49.0, 38.2, 30.8, 30.7, 30.0. HRMS m/z calcd for $C_{21}H_{20}ClNO_5Na^+$ $[M+Na]^+$: 424.0922, found 424.0924.

6.5. Bromoindole 17



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To a solution of enol ether **43**[7] (558.0 mg, 1.8 mmol) and indole **16**[1a] (881.0 mg, 2.2 mmol) in CH_2Cl_2 (40.0 mL) at −78 °C was added $SnCl_4$ (0.42 mL, 3.6 mmol). The solution turned orange red and was stirred for 50 min. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$ (8 mL) and allowed to warm to room temperature. The mixture was filtered through Celite® and added to a separatory funnel. The organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated to give a white foam that was a >10:1 diastereomeric ratio as determined by ^1H NMR. The crude product was purified by flash chromatography using 100:1 toluene/ether as eluent to afford 537.0 mg of pure **17** (48%) as a white solid. IR (neat film, NaCl) 2969, 2931, 1726, 1715, 1456, 1406, 1369, 1280, 1176, 1149, 1090, 962 cm^{-1}. ^1H NMR (C_6D_6 at 323 K) δ 8.14 (1H, d, J=8.1 Hz), 7.60 (1H, br s), 7.54 (2H, br d, J=6.3 Hz), 7.25 (1H, d, J=7.8 Hz), 6.69 (2H, d, J=7.6 Hz), 6.66 (1H, t, J=8.1 Hz), 5.48 (1H, dd, J=17.6, 11.0 Hz), 5.14 (1H, d, J=17.6 Hz), 4.95 (1H, d, J=11.0 Hz), 4.88 (1H, br m), 4.13 (1H, dd, J=13.1, 5.6 Hz), 2.48 (1H, d, J=13.5 Hz), 2.28 (1H, d, J=13.5 Hz), 1.92 (3H, br s), 1.85 (3H, s), 1.8–1.7 (2H, m), 1.38 (3H, m), 0.89 (9H, br s), 0.83 (3H, s). ^{13}C NMR (C_6D_6 at 323 K) δ 207.8, 176.8, 145.0, 142.7, 139.1, 135.5, 131.3, 130.3, 129.3, 126.8, 126.5, 125.1, 115.5, 114.2, 114.0, 73.7, 49.7, 49.5, 46.4, 38.8, 36.2, 30.8, 30.1, 27.5, 27.1, 24.9, 21.1. HRMS m/z calcd for $C_{32}H_{38}BrNO_5SNa^+$ $[M+Na]^+$: 650.1546, found 650.1547.

6.6. *N*-Methyl indole 18

To a solution of **17** (760.0 mg, 1.21 mmol) in EtOH (35.0 mL) was added crushed KOH (1.35 g, 24.0 mmol). The solution was heated at 60 °C for 40 min and monitored by TLC. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (20 mL), and extracted with EtOAc (3×20 mL). The organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated to give a brown solid. The crude product was dissolved in toluene (33 mL). Tetrabutylammonium hydroxide (40% aqueous solution, 2.5 mL, 3.8 mmol) and MeI (2.5 mL, 40.0 mmol) were added. The mixture was stirred at room temperature until the reaction was complete as judged by TLC (ca. 2 h). After completion, 10% aqueous solution HCl (20 mL) was added along with saturated aqueous NH_4Cl (20 mL), and the mixture was extracted with 1:1 hexanes/Et_2O (3×50 mL). The organic layers were combined, washed with brine (80 mL), dried (Na_2SO_4), and concentrated to give a white foam. The crude product was purified by flash chromatography using 8:1 hexanes/EtOAc as eluent to provide 490.0 mg of **18** (83% over two steps). Pure material was obtained by crystallization from benzene/hexanes. IR (neat film, NaCl) 2971, 2933, 2873, 1718, 1547, 1479, 1416, 1282, 1151, 1113, 911 cm^{-1}. ^1H NMR (C_6D_6 at 323 K) δ 7.40 (1H, m), 6.8–6.7 (2H, m), 6.54 (1H, br s), 5.52 (1H, dd, J=17.6, 11.2 Hz), 5.18 (1H, d, J=17.6 Hz), 5.01 (1H, br s), 4.95 (1H, d, J=11.2 Hz), 4.43 (1H, dd, J=12.8, 5.6 Hz), 2.81 (3H, s), 2.62 (1H, d, J=13.2 Hz), 2.35 (1H, d, J=13.2 Hz), 2.16 (3H, br s), 1.90 (1H, dt, J=13.6, 2.8 Hz), 1.72 (1H, br s), 1.55 (3H, s), 1.09 (9H, s), 0.88 (3H, s). ^{13}C NMR (C_6D_6 at 323 K) δ 208.3, 177.1, 143.0, 140.4, 128.5, 125.8, 125.7, 124.3, 122.0, 115.3, 114.3, 109.2, 74.2, 54.4, 51.0, 49.8, 46.5, 39.1, 36.2, 36.1, 32.1, 31.2, 27.4, 25.0. HRMS m/z calcd for $C_{26}H_{34}BrNO_3Na^+$ $[M+Na]^+$: 510.1614, found 510.1610.

6.7. Enol carbonate 21

A solution of ketone **18** (63.0 mg, 0.13 mmol) in THF (0.5 mL) was cooled to −78 °C and a freshly prepared solution of LDA (0.16 mL, 0.16 mmol, 1 M solution in THF) was added. The pale yellow solution was stirred for 30 min then treated with HMPA (27.0 μL, 0.16 mmol), followed by methylcyanoformate (13.0 μL, 0.17 mmol). The resulting solution was stirred for 5 h then quenched with water (5 mL). The mixture was extracted with 1:1 ether/hexanes (3×10 mL) then the combined organic layers were washed with water (10 mL) and brine (10 mL). The solution was dried (Na_2SO_4) and concentrated to afford 60.0 mg (96%) of **21** as a foam that was sufficiently pure for the next reaction. IR (neat film, NaCl) 2968, 2934, 2873, 1762, 1722, 1679, 1547, 1480, 1439, 1416, 1254, 1167, 1112, 1035, 998, 919 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.37 (1H, d, J=7.5 Hz), 7.24 (1H, d, J=8.2 Hz), 7.02 (1H, br s), 6.98 (app t, J=7.5 Hz), 5.82 (1H, dd, J=16.1, 10.4 Hz), 5.15 (1H, d, J=13.0 Hz), 5.09 (1H, d, J=6.1 Hz), 4.95 (1H, br s), 4.33 (1H, br s), 3.74 (3H, s), 2.73 (3H, s), 2.27–2.24 (4H, m), 1.93–1.88 (1H, m), 1.62–1.58 (1H, m), 1.54 (3H, s), 1.37 (3H, s), 1.27 (9H, s), 1.05 (3H, s). ^{13}C NMR ($CDCl_3$) δ 178.4, 151.4 144.2, 139.5, 129.8, 128.5, 125.2, 121.6, 118.7, 115.7, 113.8 108.6, 73.3, 64.3, 54.0, 43.4, 39.1, 35.7, 32.9, 29.5, 27.4, 26.4, 24.8, 23.8, 19.1, 13.7. HRMS m/z calcd for $C_{28}H_{36}BrNO_5Na^+$ $[M+Na]^+$: 568.1669, found 568.1661.

6.8. Tetracycle 20

A flask was charged with $Pd(OAc)_2$ (3.5 mg, 0.015 mmol) and KO^tBu (5.0 mg, 0.044 mmol). The flask was purged with Ar. Tri-*tert*-butylphosphine (138.0 μL, 0.031 mmol, 0.224 M solution in toluene) was added and the mixture was stirred at room temperature for 10 min. Next, a solution of substrate **21** (12.0 mg, 0.022 mmol) in toluene (1.0 mL) was added. The suspension was stirred for 5 min, then placed in a 70 °C oil bath and stirred for 4 h. The reaction mixture was cooled to room temperature, filtered through a short plug of Celite with Et_2O (5 mL), and concentrated. The crude product was purified by flash chromatography using 4:1 hexanes/EtOAc as the eluent to provide 3.0 mg (34%) of **20**. IR (neat film, NaCl) 2968, 2928, 2871, 1725, 1705, 1606, 1479, 1456, 1419, 1367, 1284, 1257, 1163, 1033 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.19 (1H, d, J=8.2 Hz), 7.11 (1H, dd, J=8.1, 7.2 Hz), 6.98 (1H, s), 6.69 (1H, d, J=7.2 Hz), 5.01–4.88 (3H, m), 4.86 (1H, dd, J=11.5, 5.5 Hz), 3.75 (3H, s), 3.65 (1H, d, J=1.6 Hz), 2.69 (1H, d, J=8.5 Hz), 2.46 (1H, dd, J=14.0, 5.5 Hz), 1.98 (1H, ddd, J=14.0, 11.7, 8.5 Hz), 1.60 (3H, s), 1.29 (3H, s), 1.08 (3H, s), 1.02 (9H, s). ^{13}C NMR ($CDCl_3$) δ 211.3, 177.6, 142.9, 137.2, 126.6, 124.8, 124.7, 122.3, 121.7, 120.8, 113.6, 108.3, 70.0, 68.8, 59.7, 48.3, 38.6, 35.7, 35.6, 32.9, 27.9 27.6, 26.9, 17.3. HRMS m/z calcd for $C_{26}H_{32}NO_3Na^+$ $[M+Na]^+$: 430.2353, found 430.2350.

6.9. Pentacycle 31

To a solution of PhSeCl (6.0 mg, 0.031 mmol) in 0.5 mL DCM at 0 °C (ice bath) was added tetracycle **25**[1b] (10.0 mg, 0.021 mmol) in 0.5 mL DCM and the reaction mixture was stirred at 0 °C for 1 h. After 1 h, the ice bath was removed and the reaction mixture was stirred for further 0.5 h. The reaction mixture was concentrated and the crude mixture was loaded on a preparatory-TLC plate (plate size 10×10 cm, eluent 4:1 hexanes/EtOAc) to afford 7.1 mg (53%) of pentacycle **31** as white solid. Better yield of **31** was obtained when *N*-phenylselenophthalimide (NPSP) and catalytic camphor sulfonic acid (CSA) was used in place of PhSeCl. IR (neat film, NaCl): 2954, 2927, 2855, 1727, 1700, 1473, 1462, 1420, 1365, 1254, 1090, 1056 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.58 (1H, s), 7.42 (2H, d, J=7.1 Hz), 7.25–7.21 (4H, m), 7.09 (1H, d, J=8.1 Hz), 6.93 (1H, s), 4.08 (1H, d, J=4.6 Hz), 3.78 (3H, s), 3.73 (1H, br s), 3.31 (1H, dd, J=14.7, 2.5 Hz), 3.11 (1H, dd, J=14.9, 2.4 Hz), 2.72 (1H, dd, J=11.3, 7.0 Hz), 2.58 (1H, dd, J=13.7, 11.3 Hz), 2.02–1.91 (1H, m), 1.55 (3H, s), 1.50 (3H, s), 1.31 (3H, s), 0.87 (9H, s), −0.10 (3H, s), −0.23 (3H, s). ^{13}C NMR ($CDCl_3$) δ 212.8, 197.3, 136.3, 132.9, 132.8, 130.8, 129.3, 127.5, 127.1, 125.0, 123.4, 122.6, 120.4, 108.4, 74.1, 67.8, 59.2, 56.7, 55.1, 37.3, 36.3, 33.0, 32.97, 32.1, 32.0, 25.8, 23.4, 18.2, −4.6, −5.3. HRMS m/z calcd for $C_{34}H_{44}NO_3SeSi$ $[M+H]^+$: 622.2253, found 622.2251.

6.10. Enol triflate 34

A solution of dione **33**[1b] (23.0 mg, 0.066 mmol) in THF (3.5 mL) was cooled to −78 °C. KHMDS (0.5 M in toluene, 0.26 mL, 0.132 mmol) was added and the enolate solution was stirred at the same temperature for 15 min. $PhNTf_2$ (47.2 mg, 0.132 mmol) in THF (1.5 mL) was then added and the reaction was followed by TLC. After 30 min, the reaction was quenched with 1 mL aqueous saturated solution of $NaHCO_3$ and extracted with EtOAc (3×10 mL). Combined organic layers were dried ($MgSO_4$) and concentrated. The crude material was purified via column chromatography (6:1→3:1 hexanes/EtOAc) to obtain 21.4 mg (68%) of enol triflate **34** as a yellow solid. IR (neat film, NaCl): 2924, 2854, 1736, 1704, 1451, 1418, 1378, 1334, 1246, 1214, 1140, 1028, 1012 cm^{-1}. ^1H NMR ($CDCl_3$) δ 9.66 (1H, s), 7.35 (1H, d, J=8.0 Hz), 7.23 (1H, d, J=8.0 Hz), 7.00 (1H, s), 5.87 (1H, d, J=3.2 Hz), 5.52 (1H, dd, J=17.6, 10.4 Hz), 5.42 (1H, d, J=10.4 Hz), 5.41 (1H, d, J=17.6 Hz), 3.80 (3H, s), 3.19 (1H, d, J=3.2 Hz), 1.71 (3H, s), 1.64 (3H, s), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$) δ 207.4, 194.1, 151.9, 137.9, 134.9, 126.6, 125.7, 123.5, 120.8, 120.6, 119.2, 118.7, 115.8, 110.3, 73.1, 60.1, 50.4, 36.7, 33.6, 33.1, 28.8, 21.0, 14.2. HRMS m/z calcd for $C_{23}H_{22}F_3NO_5SNa^+$ $[M+Na]^+$: 504.1063, found 504.1059.

6.11. Pentacycle 36

To a bright red THF (0.2 mL) solution of $Ru(acac)_3$ (1.0 mg, 0.0025 mmol) was added LiCl (2.0 mg, 0.047 mmol) and the reaction vessel was purged with N_2. EtMgBr (0.01 mL, 1.0 M in THF, 0.01 mmol) was added and the reaction mixture turned dark brown. The reaction mixture was stirred at ambient temperature for 15 min at which point a 0.5 mL THF solution of triflate **34** (5.0 mg, 0.01 mmol) was added and the reaction mixture was again purged with N_2 and placed in an oil bath preheated to 60 °C. After 20 h, the reaction mixture was cooled to ambient temperature and filtered over a 1″ silica plug (pipette) and concentrated. The crude material was purified via preparatory-TLC (plate size 10 cm×10 cm; eluent 4:1 hexanes/EtOAc) to afford pentacycle **36** as a white solid (50–70%). IR (neat film, NaCl): 2959, 2922, 2853, 1752, 1716, 1465, 1446, 1419, 1376, 1365, 1251, 1208, 1143 cm^{-1}. ^1H NMR ($CDCl_3$) δ 10.06 (1H, s), 7.04 (1H, d, J=8.0 Hz), 6.92 (1H, d, J=8.0 Hz), 6.89 (1H, s), 6.08 (1H, d, J=1.4 Hz), 5.70 (1H, d, J=9.0 Hz), 3.71 (3H, s), 3.52 (1H, d, J=19.8 Hz), 3.23 (1H, dd, J=19.8, 9.0 Hz), 3.18 (1H, br s), 1.91 (3H, s), 1.68 (3H, s), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$) δ 211.0, 198.1, 141.8, 136.1, 130.5, 130.2, 129.8, 129.7, 127.7, 125.9, 123.1, 122.8, 121.9, 108.1, 74.1, 64.6, 41.4, 34.4, 33.6, 33.0, 32.9, 20.8. HRMS m/z calcd for $C_{22}H_{21}NO_2Na$ $[M+Na]^+$: 354.1465, found 354.1463.

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Supplementary data

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25. This axiom is a variation of Woodward's pithy statement: "…there are no general reactions." See: Woodward, R. B. In *Proceedings of the Robert A. Welch Foundation Conference on Chemical Research, XII*; Milligan, W. O., Ed.; Organic Synthesis; 1969; pp 3–6 Huston, TX.