Natural Product Synthesis

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Synthesis of (±)-Tetrapetalone A-Me Aglycon**

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Abstract: *The first synthesis of (±)-tetrapetalone A-Me aglycon is described. Key bond-forming reactions include Nazarov cyclization, a ring-closing metathesis promoted with complete diastereoselectivity by a chiral molybdenum-based complex, tandem conjugate reduction/intramolecular aldol cyclization, and oxidative dearomatization.*

Tetrapetalones (**1**–**4**, Figure 1) were isolated by Hirota and co-workers from *Streptomyces* sp. USF-4727, a strain of bacteria in the soil of Japan.[1] With a core containing four fused rings, including a *p*-quinol, a tetramic acid, and four contiguous stereocenters, these natural products represent a unique synthetic challenge. They also exhibit moderate inhibitory activity ($IC_{50} = 190$–$360\ \mu M$) against soybean lipoxygenase (SLO). Since human lipoxygenases (HLOs) are implicated in a number of inflammatory diseases,[2] and the catalytic domain of plant and mammalian lipoxygenases is highly conserved,[3] the study of SLO inhibitors like the tetrapetalones could lead to the identification of new HLO inhibitors.

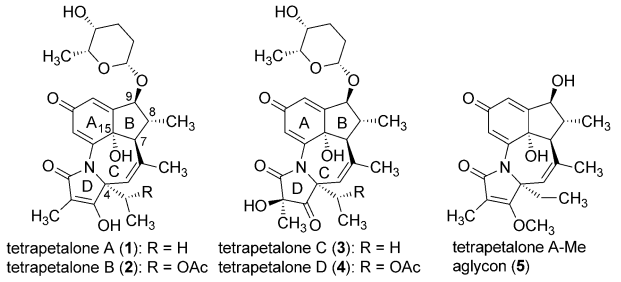
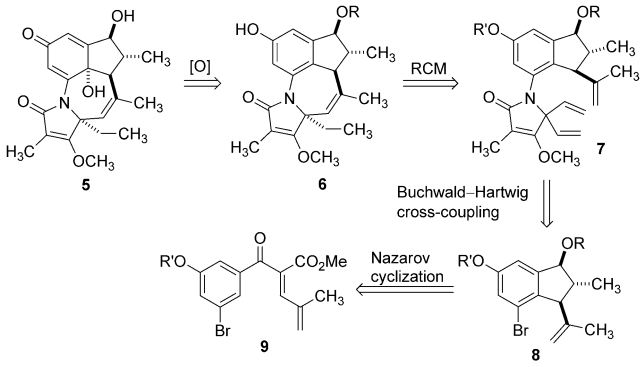


Figure 1. Structures of tetrapetalones A–D (**1**–**4**) and derivative **5**.

To aid with structural determination, Hirota and co-workers derivatized tetrapetalone A by first treating with diazomethane followed by acidic hydrolysis to furnish tetrapetalone A-Me aglycon (**5**; Figure 1).[1c] To date, there are no reported total syntheses of the tetrapetalones, though studies toward the total synthesis of the tetrapetalones have been disclosed by the research groups of Porco,[4] Hong,[5] Sarpong,[6] and Pettus.[7]

The crucial elements of our retrosynthetic analysis of **5** are shown in Scheme 1. We projected that late-stage generation of the *para*-quinol A ring could be achieved through oxidative dearomatization of the phenol **6**,[8] and envisioned that the seven-membered C ring might be accessed by a somewhat challenging diastereoselective ring-closing metathesis (RCM) involving the sterically hindered alkenes of **7**.[9] The requisite triene would be prepared through a cross-coupling[10] reaction between the aryl bromide **8** and an appropriately functionalized amine. The aryl bromide **8** could be formed from the Nazarov cyclization[11] of the aryl dienone **9**.



Scheme 1. Retrosynthetic analysis of **5**.

The synthesis commenced with the protection of the known phenol **10**[12] as the triisopropylsilyl (TIPS) ether and subjecting the product to Negishi coupling with methyl propiolate[13] to furnish the alkynoate **11** (Scheme 2). This material was heated with the nitrone **12** to generate the [3+2] cycloadduct **13**, which was then oxidized to furnish the aryl dienone **14** as an inseparable mixture of double-bond isomers (1.7:1) in 87% overall yield.[14] Nazarov cyclization of this mixture using aluminum chloride[15] produced the indanone **15** as a mixture of *anti/syn* diastereomers [3.6:1 diastereomeric ratio (d.r.)]. The new carbon–carbon bond was formed exclusively at the position *para* to the triisopropylsiloxy group, in accord with findings of Marcus and Sarpong.[6] The protodesilylation of the vinyl trimethylsilane is attributed to

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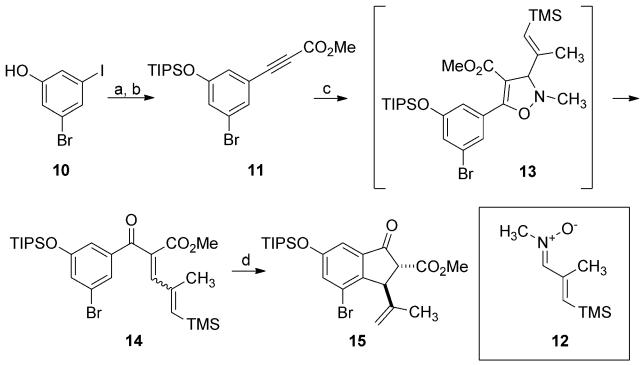
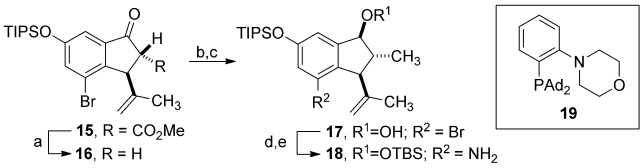


Scheme 2. Synthesis of bicycle **15**. a) TIPSCl, imidazole, THF, RT, 99% yield; b) $[Pd(PPh_3)_2Cl_2]$, $ZnBr_2$, methyl propiolate, Et_3N, THF, 60°C, 75% yield; c) **12**, $PhCH_3$, 80°C; then *m*-CPBA, CH_2Cl_2, 0°C, 87% yield (1.7:1 mixture of double bond isomers); d) $AlCl_3$, DCE, 0°C, 79% yield (ratio of *anti*/*syn* isomers = 3.6:1). DCE = 1,2-dichloroethane, *m*-CPBA = *meta*-chloroperbenzoic acid, THF = tetrahydrofuran, TIPS = triisopropylsilyl, TMS = trimethylsilyl.

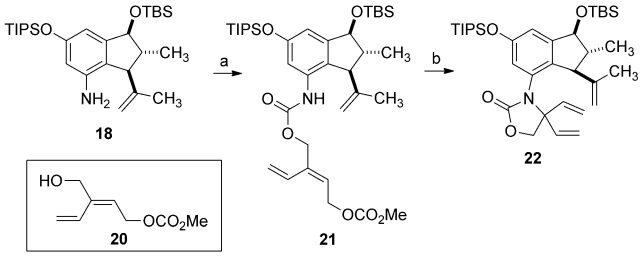
the presence of trace amounts of Brønsted acid in the reaction mixture.[16] This desilylation was an unexpected, but convenient means of revealing the terminal alkene needed for the anticipated RCM.

Next, **15** was subjected to a modified Krapcho decarboxylation in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO)[17] to furnish the indanone **16** in 91% yield (Scheme 3). Ketone α-methylation was completely diastereo-



Scheme 3. Synthesis of the aniline **18**. a) DABCO, $PhCH_3$, H_2O, 80°C, 91% yield; b) LDA, CH_3I, THF, −40°C to RT; c) $NaBH_4$, MeOH, 0°C, 67% yield over two steps; d) TBSCl, imidazole, THF, RT, 91% yield; e) $[\{Pd(allyl)Cl\}_2]$, **19**, NaO*t*Bu, NH_3, 1,4-dioxane, $PhCH_3$, 110°C, 97% yield. Ad = 1-adamantyl, DABCO = 1,4-diazabicyclo[2.2.2]octane, LDA = lithium diisopropylamine, TBS = *tert*-butyldimethylsilyl.

selective, thus occurring *anti* to the isopropenyl group on the B ring. Reduction of the ketone afforded **17** as a single diastereomer, thus indicating that hydride reduction occurs *syn* to the α-methyl group. X-ray crystallographic analysis indicated that **17** possessed the desired relative stereochemistry at C7, C8, and C9 (see the Supporting Information), and indicates that the hydride reduction occurs *syn* to the α-methyl group.[6b] The secondary alcohol in **17** was protected as the *tert*-butyldimethylsilyl (TBS) ether in preparation for Buchwald-Hartwig cross-coupling to install the C–N bond. However, under standard reaction conditions[10] cross-coupling attempts with various primary and secondary amines gave only trace amounts of the desired products. We attributed this to steric congestion in the vicinity of the C–Br bond, and hypothesized that a smaller coupling partner,



Scheme 4. Synthesis of tetracycle **22**. a) $C(O)Cl_2$, $PhCH_3$, aq. $NaHCO_3$, CH_2Cl_2, 0°C; then **20**, DMAP, CH_2Cl_2, 0°C, 69% yield; b) $[Pd(PPh_3)_4]$, THF, 40°C, 71% yield. DMAP = 4-*N*,*N*-dimethylaminopyridine.

such as NH_3, could overcome these steric issues. Indeed, the aniline **18** could be prepared from **17** in an excellent yield of 97% by using the protocol of Stradiotto and co-workers.[18] The next goal was to generate a divinyl precursor analogous to **7** (Scheme 1) to form the C ring through an RCM reaction.

The first step toward this end was the conversion of **18** into the corresponding isocyanate, which was trapped with the allylic alcohol **20** to furnish **21** (Scheme 4). This transformation was performed in preparation for an intramolecular allylic amination, which would produce a *gem*-divinyl functionality. Berkowitz and co-workers have demonstrated intramolecular allylic aminations with simple allylic carbonates,[19] but we are not aware of examples of cyclizations executed on dienyl carbonates such as **21**. The reaction proceeded smoothly to afford the divinyl oxazolidinone **22** in 71% yield, presumably via a π-pentadienyl palladium(II) intermediate.

Following the strategy outlined in Scheme 1, we examined a range of complexes (Figure 2) which might promote efficient and diastereoselective formation of the C ring

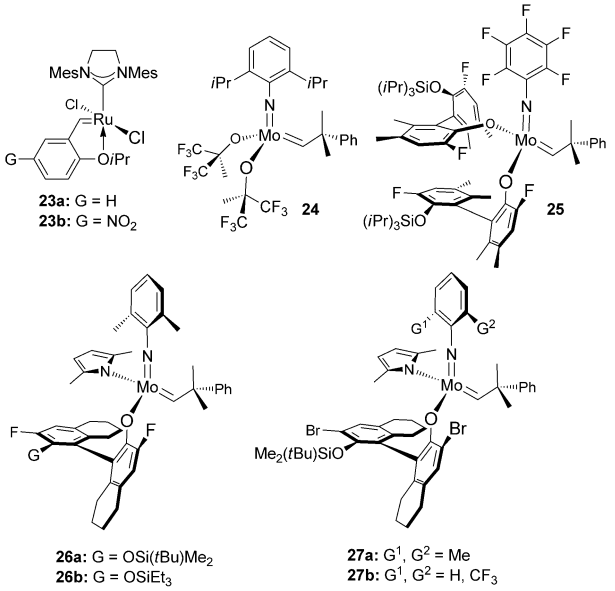
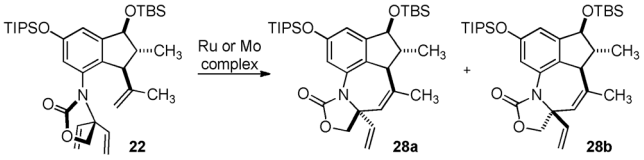


Figure 2. Representative ruthenium- and molybdenum-based complexes examined for diastereoselective RCM of **22** to afford **28a**; Mes = 2,4,6-trimethylphenyl.

Table 1: Examination of ruthenium- and molybdenum-based complexes for diastereoselective conversion of triene **22** into the tetracyclic dienes **28a**/**28b**.[a]



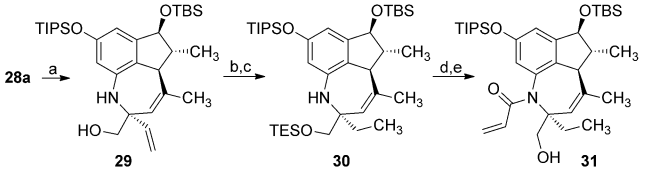
Entry	Catalyst (mol%)	*T* [°C]	*t* [h]	Conv. [%][b]	Yield [%][c]	Ratio **28a**/**28b**[b]
1	**23a** (25)	80	24	<2	–	–
2	**23a** (90)[d]	85	9	89[f]	58	2.4:1
3	**23b** (75)[e]	80	36	77[f]	56	2.4:1
4	**24** (25)	22	25	12	n.d.	1:5
5	**25** (12.5)	22	25	98	90	1:3
7	**26a** (25)	22	25	50	n.d.	>25:1
8	**26a** (25)	40	25	63	63	>25:1
9	**26b** (25)	25	25	58	n.d.	>25:1
10	**26b** (25)	65	20	83[f]	82	>25:1
11	**27a** (25)	22	25	28	n.d.	>25:1
12	**27b** (25)	22	25	49	40	1:1

[a] Reactions were performed under N_2 in toluene (0.015 M–0.05 M for entries 1–3) or benzene (0.1–0.13 M for entries 4–11). [b] Determined by analysis of the 400 MHz ^{1}H NMR spectra of the unpurified mixtures. [c] Yield of isolated and purified products. [d] Initial loading was 5 mol% with an additional 5 mol% introduced every 30 min. [e] Initial loading was 25 mol% and an additional 25 mol% was introduced every 12 h. [f] Determined by isolation and purification of products and unreacted starting materials. n.d. = not determined.

through catalytic RCM. Representative cases are illustrated in Table 1. In the presence of 25 mol% of the carbene **23a**,[20] none of the ring-closed product was observed even at 80°C after 24 hours (Table 1, entry 1). It was only with a total of 90 mol% of the ruthenium complex, introduced over 9 hours, that 89% conversion into a 2.4:1 mixture of **28a** and **28b** was obtained (58% yield; entry 2). Use of the derivative **23b**, which initiates metathesis faster,[21] did not lead to improvement in efficiency or stereoselectivity (entry 3). With the molybdenum-based bis(alkoxide) **24**,[22] only 12% conversion was observed after 25 hours at ambient temperature, presumably because of the relatively facile decomposition of the alkylidene (entry 4). Notably, however, the undesired diastereomer (**28b**) was generated preferentially in this experiment. Somewhat disconcertingly, the opposite sense of diastereoselectivity between ruthenium carbenes and dioxy-Mo alkylidenes was confirmed with the finding that 12.5 mol% of the bis(aryloxide) **25**[23] delivered 98% conversion into a 1:3 mixture of **28a** and **28b** (90% yield, 25 h, 22°C; entry 5).

We next probed the activity of molybdenum-based monoaryloxide pyrrolide (MAP) complexes.[24] Use of the complex **26a**[25] at 22°C afforded the desired isomer **28a** exclusively (<2% **28b**; entry 7, Table 1). At elevated temperature (40°C), **28a** was isolated in 63% yield (63% conv.) without any detectable loss of stereoselectivity (entry 8). Further screening allowed us to determine that the MAP neophylidene **26b** gives rise to a more desirable catalyst (entries 9–10). At 65°C and in the presence of 25 mol% of the in situ generated **26b**, 1.5 grams of the triene **22** was transformed into **28a** in 82% yield (83% conv.) and in greater than 25:1 d.r. Several additional observations regarding the diastereoselective RCM merit note: 1) Use of racemic MAP complexes suffice; enantiomerically pure alkylidenes are similarly diastereoselective, but gave little or no kinetic resolution, 2) with 10 mol% and 15 mol% **26b**, under otherwise the identical reaction conditions as illustrated in entry 10 of Table 1, 56 and 73% conversion, respectively, was observed (>25:1 **28a**/**28b**), 3) changes in the identity of the MAP complex can engender substantial variations in efficiency and stereoselectivity, as was seen in experiments with **27a**,**b** (entry 11–12 of Table 1). The mechanistic rationale for such selectivity fluctuations are the subject of ongoing investigations and will be disclosed in the full account of this work. 4) Although catalytic diastereoselective RCM has been previously examined and utilized in natural product synthesis,[26] we know of no other examples in which a chiral catalyst has been used to enhance the substrate-controlled level of selectivity (i.e., from 2.4:1 to >25:1) in an olefin metathesis reaction.

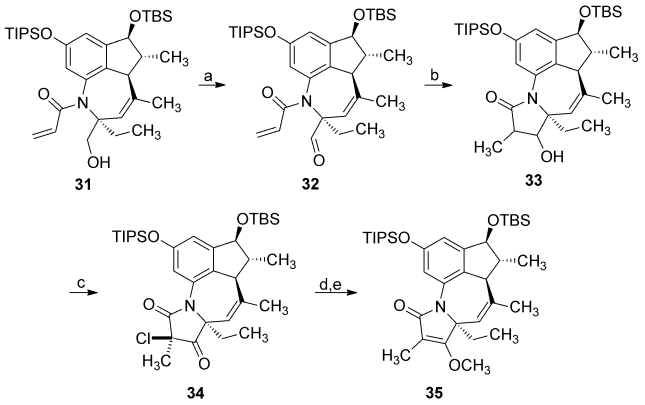
The completion of the synthesis of the D ring commenced with the reduction of **28a**, using an excess of $LiEt_3BH$,[27] to secure the amino alcohol **29** in 80% yield (Scheme 5). The alcohol **29** was then protected as the triethylsilyl (TES) ether,



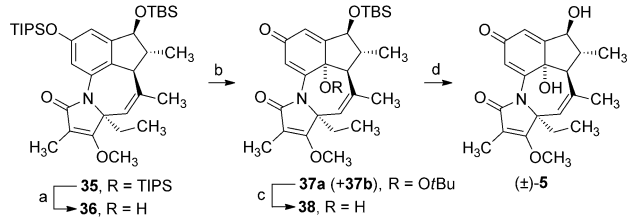
Scheme 5. Synthesis of the alcohol **31**. a) $LiEt_3BH$, THF, 0°C, 80% yield; b) TESCl, imidazole, DMF, 40°C, 88% yield; c) $[RhCl(PPh_3)_3]$, 1 atm H_2, $PhCH_3$, 92% yield; d) acryloyl chloride, DIEPA, 4 Å M.S., $PhCH_3$, 50°C; e) HCl, H_2O, MeOH, THF, RT, 71% over two steps. DIEPA = *N*,*N*-diisopropylethylamine, DMF = *N*,*N*-dimethylformamide, M.S. = molecular sieves, TES = triethylsilyl.

and chemoselective hydrogenation with Wilkinson's catalyst[28] furnished the cyclic amine **30** in 92% yield. The amine **30** was acylated with acryloyl chloride[29] and then subjected to acid-promoted removal of the TES group to furnish the alcohol **31** in 71% yield over two steps. Notably, the alcohol **31** can be prepared on gram scale using this strategy.

To complete the assembly of the D ring, **31** was subjected to Ley oxidation conditions[30] to produce the aldehyde **32** (Scheme 6) in 86% yield. To close the ring, we performed a tandem conjugate reduction/intramolecular aldol cyclization.[31] Treatment of **32** with Stryker's reagent smoothly furnished the tetracycle **33** as a mixture of four diastereomers in a 94% combined yield.[32] Swern oxidation[33] of **33** furnished the chlorinated tetracycle **34** in 74% yield as a single isomer, an unexpected but precedented result.[34] Dechlorination with zinc and acetic acid[35] proceeded smoothly to furnish a tetramic acid which was methylated with (trimethylsilyl)diazomethane[36] to afford the tetracycle **35** in 61% yield over two steps.



Scheme 6. Synthesis of the tetracycle **35**. a) TPAP, NMO, 4 Å MS, CH_2Cl_2, CH_3CN, 0 °C, 86% yield; b) $[PPh_3CuH]_6$, $PhCH_3$, 0 °C, 94% yield; c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 °C to RT, 74% yield; d) Zn, HOAc, CH_2Cl_2, RT; e) $(TMS)CHN_2$, MeOH, $CHCl_3$, RT, 61% yield over two steps. DMSO = dimethyl sulfoxide, NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetrapropylammonium perruthenate.



Scheme 7. Synthesis of (±)-**5**. a) TBAF(tBuOH)$_4$, THF, RT, quant. yield; b) $[Rh_2(Cap)_4]$, tBuOOH, DCE, 78 °C, 1.3:1 d.r. (**37a**/**37b**), 84% yield; c) 10% Cd/Pb couple, THF, 1 M aq. NH_4OAc, RT, 76% yield; d) HF/pyridine, THF, RT, 61% yield. Cap = caprolactamate, TBAF = tetrabutylammonium fluoride.

Chemoselective deprotection of the phenol in **35** was achieved with tetrabutylammonium tetra(*tert*-butyl alcohol)-coordinated fluoride,[37] thus producing **36** (Scheme 7). The crucial oxidative dearomatization was not as straightforward as we had anticipated: treatment of the phenol **36** with (diacetoxyiodo)benzene (PIDA) and [bis(trifluoroacetoxy)-iodo]benzene (PIFA)[38] failed to give the desired *para*-quinol.[39] However, treatment of **36** with tBuOOH and dirhodium caprolactamate $[Rh_2(Cap)_4]$[40] did generate peroxide **37a** along with its C15 epimer **37b** (1.3:1 d.r.) in 84% combined yield. Cleavage of the O–O bond of **37a**/**37b** was attempted using Zn^0/HOAc, Mg^0/MeOH,[41] and Al amalgam,[42] but the only reaction observed was the regeneration of **36**. Fortunately, peroxides **37a** and **37b** could be separated by column chromatography and ultimately, treatment of **37a** with 10 mol% Cd/Pb couple[43] led to successful cleavage of the peroxide to furnish the *para*-quinol **38** in 76% yield. The undesired peroxide **37b** could be recycled via **36**, as described above. Finally, deprotection of **38** with HF/pyridine afforded (±)-tetrapetalone A-Me aglycon [(±)-**5**].

The ^{1}H NMR spectrum obtained for (±)-**5** matches that reported by Hirota and co-workers.[1c,44] Furthermore, a single-crystal X-ray diffraction experiment unambiguously established the structure of (±)-**5** (see the Supporting Information).

In summary, we have developed an effective strategy for the synthesis of (±)-tetrapetalone A-Me aglycon. Key bond-forming reactions include Nazarov cyclization to form the B ring, diastereoselective ring-closing metathesis to form the seven-membered C ring, a tandem conjugate reduction/intramolecular aldol cyclization to form the D ring, and an oxidative dearomatization to form the *para*-quinol A ring. Notably, the stereochemistry at C4, C8, C9, and C15 was relayed from the stereogenic center at C7, which was installed by Nazarov cyclization. Furthermore, the exceptional diastereoselectivity observed in the RCM reaction furnishing the C ring underscores the role that chiral catalysts can play in providing levels of efficiency as well as stereoselectivity which may not be accessible through the use of achiral complexes.[45] Development of a strategy for the enantioselective synthesis of the tetrapetalones is underway.

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