Organic LETTERS

Letter

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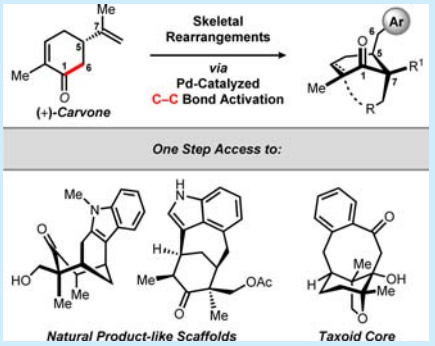
Construction of Enantiopure Taxoid and Natural Product-like Scaffolds Using a C−C Bond Cleavage/Arylation Reaction

Manuel Weber, Kyle Owens, Ahmad Masarwa,* and Richmond Sarpong*

Department of Chemistry, University of California—Berkeley, Berkeley, California 94720, United States

Supporting Information

ABSTRACT: An approach to construct enantiopure complex natural product-like frameworks, including the first reported synthesis of a C17 oxygenated taxoid scaffold, is presented. A palladium-catalyzed C−C activation/cross-coupling is utilized to access these structures in a short sequence from (+)-carvone; the scope of this reaction is explored.



Small, abundant, enantioenriched secondary metabolites termed the "chiral pool"[1] have long been recognized as an excellent starting point for the enantiospecific preparation of many complex molecules.[2] Carvone (**1**) is one such compound, which has been shown to undergo a rich assortment of transformations that have led to the preparation of numerous natural products[3] and their analogues. Recently, synthesis of natural product inspired compounds, with structures that are reminiscent of known biologically active compounds, has provided a way to synthesize compound libraries with increased opportunities to access a desired biological activity.[4,5] Many applications of chiral pool compounds for complex molecule synthesis have employed traditional manipulations that retain the same carbocyclic skeleton.[6] Complementary methods that accomplish the deep-seated reorganization of the carbon framework would be of great utility in synthetic chemistry. The products of these rearrangements could facilitate the synthesis of a wide variety of structures that are only distantly related to the initial natural product and may possess enhanced biological activities.

Methods that may achieve this goal include selective C−H[7] and C−C[8] bond activation. The use of nontraditional functional handles (i.e., C−H and C−C bonds) has become a powerful tool for the construction of new C−C bonds. While recent advances in C−H activation/functionalization have found applications in natural product synthesis,[9] the use of C−C activation is still in its infancy in this respect.[10] In this manuscript, we describe the synthesis of natural product-like scaffolds including the core of C17 oxygenated taxoids by applying a Pd-catalyzed C−C activation/arylation reaction to readily accessible cyclobutanols.[11]

Recently we reported a strategy[12] to achieve selective C−C bond cleavage of carvone-derived cyclobutanols **2** and **3** (Scheme 1), providing access to vicodiol-type scaffolds (see **4**) through C1−C7 bond cleavage when traditional electrophiles (e.g., *m*CPBA, PPTS or NBS) were applied. Complementary to this result, several novel cyclohexenone scaffolds (e.g., **5** and **6**) that comprise the core of natural products such as drummondol (**11**), suaveolindol (**12**), and others were accessed through [Rh(I)]-mediated C1−C6 bond activation. However, using rhodium catalysts, we were unable to functionalize the substrates at C6 following C−C bond activation.[13] We sought to overcome this limitation with palladium-catalyzed cross-coupling chemistry,[14] which would set the stage for accessing a variety of interesting frameworks such as **7**−**9**.

In particular, we hypothesized that arylation at C6 could provide a rapid route to the cores of taxoids such as taxinine M (**14**).[15,16] Taxinine M and related taxoids possess a bridging ether ring that distinguishes them from most taxoid natural products. No syntheses of these natural products or their core structures have been reported to date. A straightforward route to a variety of new taxoid analogues could be useful in drug discovery efforts to identify more effective chemotherapeutic agents. With the synthesis of **7**−**9** in mind, we first sought to develop a general and broadly applicable ring-opening/aryl cross-coupling reaction of tricycle **2** (accessible in one step from **3b**) and then of **3c** in order to prepare a diverse array of interesting scaffolds.

Under the optimized conditions (Table 1; conditions A),[17] we found that the electronic nature of the aryl halide was inconsequential as the reaction tolerated both electron-donating and -accepting substituents. Further investigations revealed that ortho-substituted aryl bromide coupling partners and heteroaryl bromides bearing Lewis basic groups benefit

Received: September 26, 2015
Published: October 20, 2015

DOI: 10.1021/acs.orglett.5b02797
Org. Lett. 2015, 17, 5432−5435

Scheme 1. Complementary Strategies To Access Natural Product-Like Scaffolds from (+)-Carvone

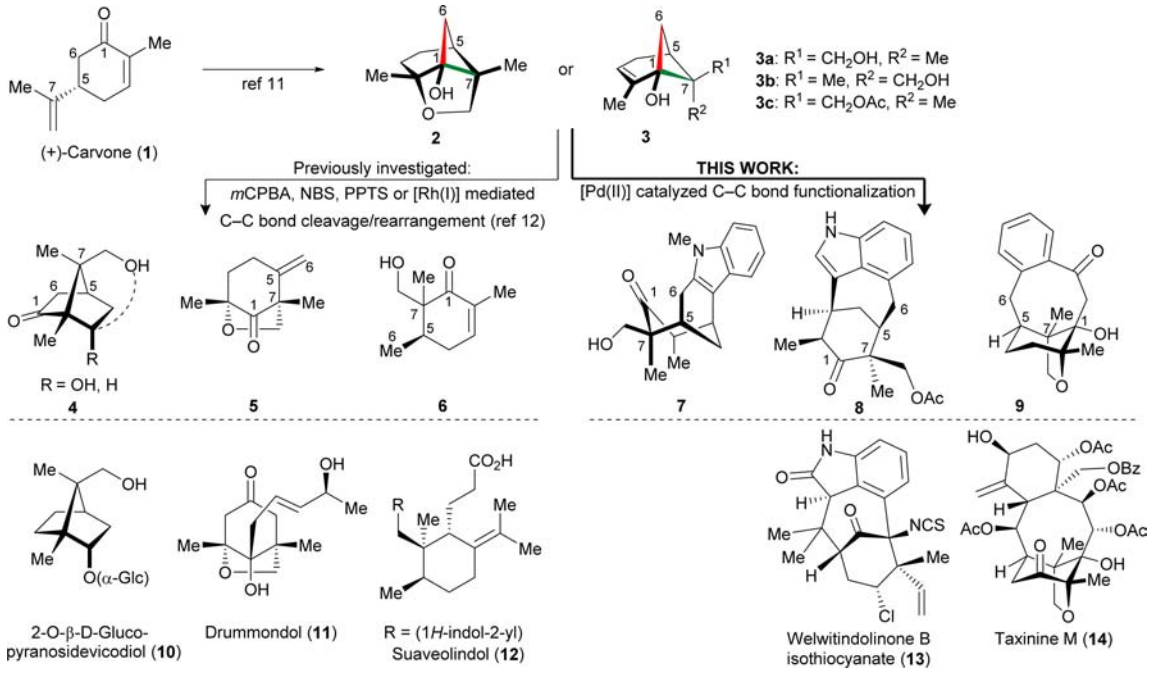
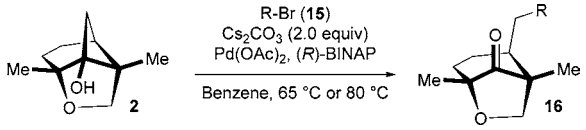


Table 1. Substrate Scope of the Ring-Opening/Cross-Coupling Reaction of 2



no.	15	R =	cond.	16	yield[a] (%)
1	a	C_6H_5	A	a	87
2	b	4-MeO-C_6H_4	A	b	89
3	c	4-O_2N-C_6H_4	A	c	85
4	d	3,5-$(MeO)_2$-C_6H_3	A	d	82
5	e	3-F-5-F_3C-C_6H_3	A	e	86
6	f	2-H_3C-C_6H_4	B	f	93
7	g	2-*i*Pr-C_6H_4	B	g	90
8[b]	h	2-Ac-C_6H_4	E	h	68
9	i	5-pyrimidinyl	D	i	70
10	j	2-thiophenyl	C	j	68
11	k	3-furyl	C	k	34
12	l	3,5-$(MeO)_2$-6-Ac-C_6H_2	E	l	59
13	m	2-(N-Me)-indoyl	D	m	54
14	n	3-pyridyl	D	n	76

[a]Yield refers to isolated yield after chromatography. [b]71% on 0.8 mmol scale. Conditions A: **15** (1.25 equiv), $Pd(OAc)_2$/(*R*)-BINAP (5 mol %), 80 °C, 4 h. Conditions B: **15** (2.0 equiv), $Pd(OAc)_2$/(*R*)-BINAP (10 mol %), 80 °C, 22 h. Conditions C: **15** (1.25 equiv), $Pd(OAc)_2$/(*R*)-BINAP (5 mol %), 65 °C, 22 h. Conditions D: **15** (1.0 equiv), $Pd(OAc)_2$/(*R*)-BINAP (15 mol %), 64 °C, 43 h. Conditions E: **15** (2.0 equiv), $Pd(OAc)_2$ (15 mol %), P(*t*Bu)$_3$ (1.5 equiv), 65 °C, 22 h.

from slight variations to the standard conditions (compare conditions A–D, Table 1). The connectivity and absolute configuration of the products is supported by single crystal X-ray analysis of **16g**.[17,18]

In order to access the taxoid core, the cross-coupling of 2′-bromoacetophenones such as **15h** and **15l** was required. These substrates proved challenging under conditions A–D described in Table 1. On the basis of our hypothesis that an unreactive palladacycle[19] could form under the standard conditions, we explored conditions to minimize this likelihood.[20] Ultimately, replacing BINAP with monodentate phosphine ligands, which are known to form highly reactive complexes with a free coordination site,[21] provided the desired cross-coupling adducts. With P(*t*Bu)$_3$ as the ligand, the ring-opening/cross-coupling products **16h** and **16l** were formed in good yields.[22]

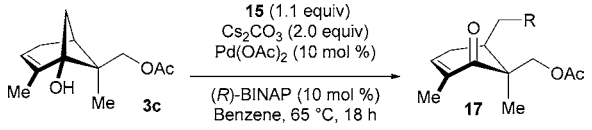
Hydroxylated pinene derivatives **3** have also been studied in the cross-coupling reaction. In our previous studies of Rh-catalyzed C–C bond activation, we observed a matched/mismatched effect depending on the absolute configurations of the cyclobutanol substrate and ligand that were employed.[12] As such, we surveyed several chiral ligands in the Pd-catalyzed ring-opening/cross-coupling of **3a** and **3c**.[23]

While the cross-coupling of **3c** exhibited only a small preference for (*R*)-BINAP over (*S*)-BINAP, the effect was more pronounced for **3a**, which lacks the acyl group on the primary hydroxyl.[17] This acyl group helps prevent decomposition of the cyclohexenone products via a retro-aldol pathway. As illustrated in Table 2, the couplings employing **3c** are also insensitive to the electronic properties of the aryl bromide, providing access to products bearing a variety of electron-donating and -withdrawing groups on the aryl moiety in good yields. Sterically encumbered and heteroaryl bromides are also tolerated, yielding cross-coupled compounds (see **17** for a general structure) in good to high yields. Notably, a vinyl bromide (**15p**) is also a competent cross-coupling partner, providing the prenylated product in up to 55% yield.

We have utilized several of the cross-coupling products (**16** and **17**) to generate structurally complex, polycyclic, natural product-like compounds (Scheme 2). For example, nucleophilic indoles (see **17m′** and **17o**) present opportunities for further C–C bond forming reactions. Specifically, intramolecular conjugate addition of **17m′** using Yb(OTf)$_3$ in acetonitrile gives tetracyclic product **7** in 83% yield,[24] whereas thermolysis of the Boc group in **17o** and subsequent treatment

DOI: 10.1021/acs.orglett.5b02797
Org. Lett. 2015, 17, 5432–5435

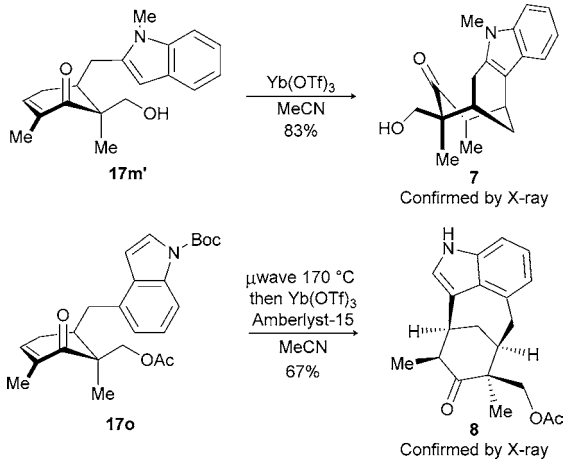
Table 2. Substrate Scope of the Ring-Opening/Cross-Coupling Reaction of 3c



no.	15	R =	17	yield[a] (%)
1	a	C_6H_5	a	64
2	b	4-MeO-C_6H_4	b	76
3	c	4-NO_2-C_6H_4	c	74
4	g	2-*i*Pr-C_6H_4	g	67
5	m	2-(N-Me)-indoyl	m	59 (29)[b]
6	o	4-(N-Boc)-indoyl	o	81
7	p	2-methylprop-1-en-1-yl	p	49 (55)[b,c]

[a]Yield refers to isolated yield after chromatography. [b]With **3a**. [c]With (*S*)-BINAP.

Scheme 2. Synthesis of Enantiopure Natural Product-like Scaffolds

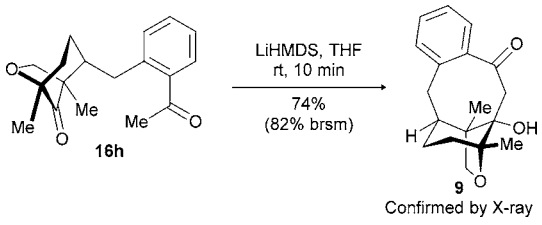


with $Yb(OTf)_3$ and an acidic resin yields **8**. The structures of **7** and **8** were both confirmed by single crystal X-ray analysis.[18] Interestingly, **8** possesses a scaffold reminiscent of the welwitindolinones (e.g., welwitindolinone B isothiocyanate, **13**).[25]

Finally, we also pursued the cyclization of acetophenone derivatives such as **16h** to access the 6−8−6 tricyclic framework found in taxoid natural products. However, several challenges had to be addressed. First, 8-membered rings possess significant transannular strain that had to be overcome.[26] In addition, ketone **16h** is flanked by two tetra-substituted α-positions, making additions into the carbonyl group difficult.

We first investigated a Mukaiyama-type cyclization process. However, after formation of a TMS-enol ether from **16h**, conditions could not be identified to give the desired cyclization product. Instead, we found that treating **16h** directly with a bis(trimethylsilyl)amide base in THF forms an equilibrium mixture favoring the open form (**16h**) over tetracycle **9**. The counterion (i.e., Li^+, Na^+, or K^+) had a significant impact on the position of the equilibrium. While Na- and KHMDS formed only trace amounts of **9** (even after 2 h), an excess of LiHMDS achieved nearly instantaneous formation of **9**. However, upon prolonged reaction, **16h** was observed as the exclusive product. Quenching the reaction mixture by the addition of water after a short period of time (~10 min) gave the desired taxoid scaffold (**9**) in high yield along with unreacted starting material (Scheme 3).

Scheme 3. Synthesis of Enantiopure Taxoid Core 9



The identity of **9** was unambiguously confirmed by X-ray analysis.[18] This short sequence serves as a highly step-economical route to the taxoid framework (five steps from (+)-carvone) and provides access to enantiomerically pure **9**. This constitutes the first synthesis of the core of C17-oxygenated taxoids such as taxinine M (**14**),[15] taxagifine,[27] and taxacin, which contain a bridging ether, that distinguishes them from other taxoids.[28]

In conclusion, we identified conditions for a sequential, ring-opening/cross-coupling reaction starting from readily accessible cyclobutanols. This reaction tolerates a broad range of aryl and heterocyclic bromides, as well as a vinyl bromide. Various steric and electronic effects of the aryl substituents are accommodated, providing a short route to several complex frameworks. In particular, intramolecular conjugate additions provided access to natural product-like polycycles **7** and **8**. The first synthesis of taxoid scaffold **9** showcases the ability of this sequence to rapidly build molecular and stereochemical complexity. Applications of this methodology to the synthesis of several natural products are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02797.

Experimental details, screening results, complete analytical data for all new compounds (PDF)
Crystallographic data for **16g** (CIF)
Crystallographic data for **9** (CIF)
Crystallographic data for **7** (CIF)
Crystallographic data for **8** (CIF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ahmadm@berkeley.edu (A.M.)
*E-mail: rsarpong@berkeley.edu (R.S.)

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the DAAD (German Academic Exchange Service) for a postdoctoral fellowship to M.W. and the Rothschild Foundation as well as VATAT (The Israeli Council for Higher Education) for postdoctoral fellowships to A.M. We thank Dr. A. DiPasquale (UC Berkeley) and Dr. L. J. Daumann (UC Berkeley) for solving the crystal structures of **16g**, **7**, **8**,

DOI: 10.1021/acs.orglett.5b02797
Org. Lett. 2015, 17, 5432−5435

and **9** (supported by NIH Shared Instrument Grant S10-RR027172).

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(17) See the Supporting Information for details.

(18) (a) CCDC 1414897 (**16g**), 1415152 (**7**), 1414899 (**8**), and 1414900 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/getstructures. (b) See the Supporting Information for visualized structures.

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(22) Competing β-hydride elimination and diminished reactivity were observed when lower ligand loadings (20−30 mol %) were used. However, with 1.5 equiv of $P(t\mathrm{Bu})_3$, higher reactivity was achieved and side product formation was reduced (see the Supporting Information for more details). This may be due to the decreased opportunities for free coordination sites on the alkyl palladium intermediate. Further optimization studies to lower the ligand loading are under investigation.

(23) Substrate **2** was found to undergo the title reaction somewhat more slowly when (*S*)-BINAP was used.

(24) The product was formed as a diastereomeric mixture at the epimerizable α-position.

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DOI: 10.1021/acs.orglett.5b02797
Org. Lett. 2015, 17, 5432−5435