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Synthesis of substituted 1-benzazepin-2-ones via ring-closing olefin metathesis

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ABSTRACT

The 1-benzazepin-2-one ring system is an important structural feature of marketed drugs, clinical candidates, and other bioactive molecules. We have developed a new benzazepinone synthesis that employs ring-closing olefin metathesis as a key step. This route provides efficient access to substituted benzazepinones that are difficult to synthesize via existing procedures.

The 1-benzazepin-2-one ring system is an important structural motif in medicinal chemistry. It is a core feature of the angiotensin converting enzyme (ACE) inhibitor Benzazepril,[1] and of clinical candidates such as the growth hormone secretagogue L-739,943,[2] and the antithrombotic agent CVS-1778[3] (Fig. 1). 1-Benzazepin-2-ones have also been employed as $Na_v1.7$ sodium channel blockers,[4] L-type ($Ca_v1.2$) calcium channel blockers,[5] and analgesics.[6]

Their utility notwithstanding, benzazepinones can exhibit pharmacokinetic liabilities due to their electron-rich nature. For instance, they have been reported to undergo metabolic oxidation at various sites (C6–C9) on the phenyl ring.[7] This oxidation can lead to higher clearance, lower exposure, and diminished efficacy when these agents are dosed in vivo. A common strategy for mitigating such oxidation involves blocking the site of metabolism, typically with an electron-withdrawing substituent such as fluorine or trifluoromethyl. A general benzazepinone synthesis that allowed facile substitution of C6–C9 could provide access to more metabolically stable therapeutic agents, and would thus be highly desirable.

Several benzazepinone syntheses have been reported to date. The parent 1,3,4,5-tetrahydro-1-benzazepin-2-one **1** has been prepared classically via Beckmann rearrangement of the oxime of α-tetralone.[8] This approach remains in use, and subsequent modifications have been reported.[9] 1-Benzazepin-2-ones have also been more recently prepared via Pd-catalyzed amidation of aryl halides,[10] Rh-catalyzed oxidative cyclization of amino alcohols,[11] oxidative cyclization of *N*-methoxyamides,[12] coupling of organozinc reagents with aryl halides,[13] and radical-mediated cyclization.[14] While these methods each have various merits, they also suffer limitations, including lack of availability of substituted starting materials, a requirement for nitrogen protection and deprotection in some methods, and lack of generality with regard to substrate.

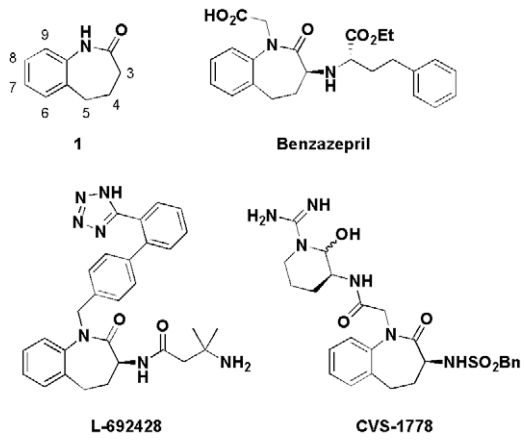

Figure 1. Benzazepinone clinical agents.

We report herein a general method for benzazepinone synthesis that employs ring-closing olefin metathesis (RCM) as a key step. This approach allows facile substitution of C6–C9 and provides the benzazepinone product in four steps from commercially available starting materials. In choosing this strategy, we were influenced by the pioneering work of Grubbs, Fürstner, and others that established RCM as a method of choice for the synthesis of seven-membered rings.[15]

In principle, the benzazepinone ring system could be constructed via metathetic bond formation between C3 and C4, or C4 and C5. To explore each possibility, we prepared model metathesis substrates **3** and **5**. As shown in Scheme 1, 4-amino-3-bromobenzotrifluoride **2** was heated in the presence of tributylvinyltin and $Pd(PPh_3)_4$ to yield the corresponding Stille coupling product. Amidation of the anilinic nitrogen with vinylacetic acid then afforded **3**. Alternatively, **2** could undergo Stille coupling with allyltributyltin and subsequent amidation with acryloyl chloride to provide metathesis substrate **5**.

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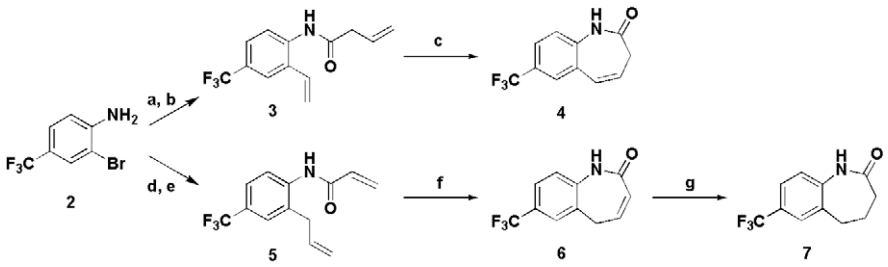


Scheme 1. Reagents and conditions: (a) 5 mol % $Pd(PPh_3)_4$, tributylvinyltin, DMF, 80 °C (89%); (b) vinylacetic acid, oxalyl chloride, DMF, CH_2Cl_2, 0 °C (66%); (c) see Table 1 for details; (d) 4 mol % $Pd(PPh_3)_4$, allyltributyltin, DMF, 80 °C (86%); (e) acryloyl chloride, triethylamine, THF, −10 °C, (70%); (f) see Table 1 for details; (g) 10% Pd:C, H_2 (1 atm), 1:1 THF:CH_3OH (82%).

With substrates **3** and **5** in hand, we were ready to test the viability of each ring closure. In these experiments, we employed second generation Grubbs, Grela, and Hoveyda type catalysts **8**, **9**, and **10** (Fig. 2). These were selected on the basis of their established high levels of reactivity and stability, and because they were expected to offer differential and perhaps complementary reactivity patterns relative to one another. Reactions were conducted under standard RCM conditions—either at room temperature in dichloromethane, or at 70 °C in toluene.

We began this series of experiments by exploring bond formation between C4 and C5. As shown in Table 1, exposure of metathesis substrate **3** to 5 mol % of **8**, either at room temperature (entry 1) or with heating (entry 2), afforded no yield of desired product **4**. An increase in the catalyst loading to 20 mol % did furnish **4**, albeit in a modest 35% yield (entry 3). Indenylidene catalyst **9** also proved ineffective in converting **3** to **4** (entries 4 and 5). The Hoveyda type catalyst **10**, on the other hand, delivered a moderate yield of desired product when the reaction was run at room temperature (entry 6). Unfortunately, heating did not improve the yield, even when a higher catalyst loading was employed (entry 7).

In contrast, bond formation between C3 and C4 proceeded much more readily. Thus, exposure of substrate **5** to 5 mol % of **8** or **10** delivered the desired product **6** in 65% and 89% yields, respectively (entries 8 and 9). Simple balloon hydrogenation of **6** then furnished the saturated 1-benzazepin-2-one **7** (Scheme 1). On the basis of these findings, it appeared that an optimal metath-

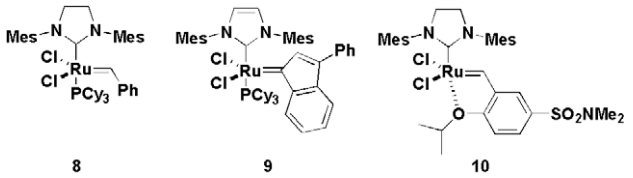


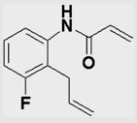
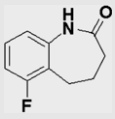
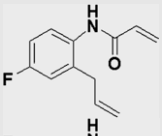
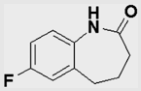
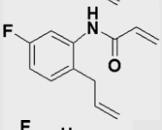
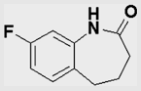
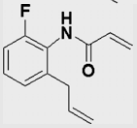
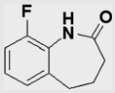
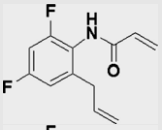
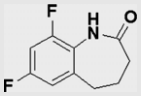
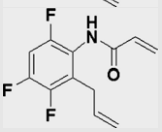
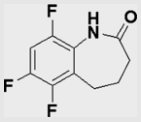
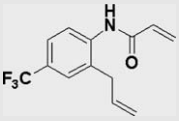
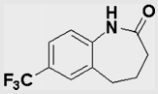
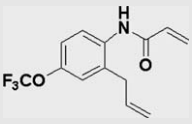
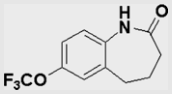
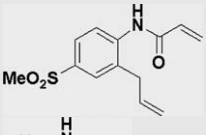
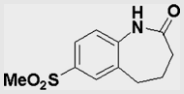
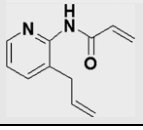
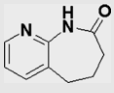
Figure 2. Second generation metathesis catalysts.

Table 1
Optimization of RCM reactions shown in Scheme 1

Entry	Reaction	Conditions[a]	Yield (%)
1	**3** to **4**	5 mol % 8, dichloromethane, rt	0
2	**3** to **4**	5 mol % 8, toluene, 70 °C	0
3	**3** to **4**	20 mol % 8, toluene, 70 °C	35
4	**3** to **4**	5 mol % 9, dichloromethane, rt	0
5	**3** to **4**	5 mol % 9, toluene, 70 °C	0
6	**3** to **4**	5 mol % 10, dichloromethane, rt	42
7	**3** to **4**	20 mol %10, toluene, 70 °C	43
8[b]	**5** to **6**	5 mol % 8, dichloromethane, rt	65
9	**5** to **6**	5 mol % 10, dichloromethane, rt	89

[a] Reactions were stirred for 18 h unless otherwise indicated.
[b] Reaction complete after 2 h.

Table 2
Benzazepinone synthesis via two-step RCM/hydrogenation sequence

Entry[a]	Substrate	Product	Yields[b] (%)
1			87, 92
2			67, 77
3			80, 81
4			73, 32
5			60, 79
6			87, 91
7			89, 82
8			69, 97
9			86. 90
10			0

[a] RCM reactions were conducted using 5 mol % 10 in dichloromethane at room temperature. Hydrogenations were conducted under 1 atm hydrogen with 10% Pd:C as catalyst in 1:1 tetrahydrofuran:methanol.
[b] Yields are shown as (X%, Y%) and are for RCM and hydrogenation reactions, respectively.

esis procedure would involve the use of catalyst **10** to effect bond formation between C3 and C4.

With the site of ring closure established, we next explored the generality of this strategy. We were most interested in probing the synthesis of electron-deficient benzazepinones, as clinical agents that incorporated these would likely be more resistant to metabolic oxidation. Additionally, electron-deficient substrates might prove challenging for existing benzazepinone syntheses, many of which proceed via oxidative mechanisms or cationic intermediates. As shown in Table 2, substrates that incorporated fluorine at the nascent 6, 7, 8, or 9 positions underwent metathesis and subsequent hydrogenation in good yields to provide the corresponding fluorinated benzazepinones (entries 1–4). Di- and trifluorinated substrates could also be employed (entries 5 and 6), as could those bearing stronger electron-withdrawing groups such as trifluoromethyl (entry 7), trifluoromethoxy (entry 8), and methyl sulfone (entry 9). Note that many of these sequences were conducted on multigram scale, thus confirming the practicality of this approach.

A final example (entry 10) illustrates the one limitation of this method that we have encountered thus far, namely its incompatibility with substrates that contain basic heteroatoms. Exposure of the pyridinyl substrate shown to 5 mol % of **10**, either at room temperature in dichloromethane or at 70 °C in toluene, resulted in no conversion to desired product. Similar results were obtained with catalysts **8** and **9**. The incompatibility of Rh-based RCM catalysts with substrates that can coordinate to the metal center is, by now, well documented, and likely accounts for the lack of reactivity observed in this case.[16]

In summary, we have developed a new synthesis of 1-benzazepin-2-ones that employs ring-closing olefin metathesis as a key step. This route delivers benzazepinone products in four steps from commercially available starting materials, and can be used preparatively on multigram scale. Importantly, it provides access to a range of substituted benzazepinones that are otherwise difficult to synthesize. Future work will be aimed at further expanding the reaction scope, and will be reported in due course.

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Supplementary data

Representative experimental procedures for the synthesis of 7-fluoro-1,3,4,5-tetrahydro-1-benzazepin-2-one (Table 2, entry 2) are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.022.

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