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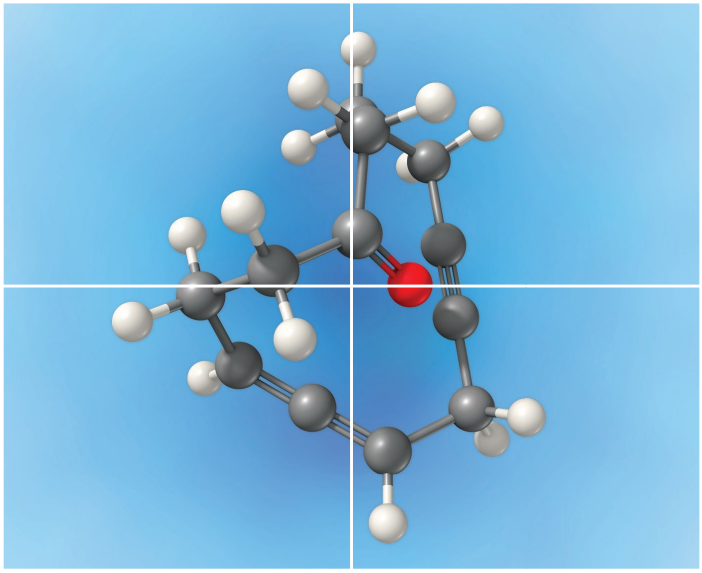

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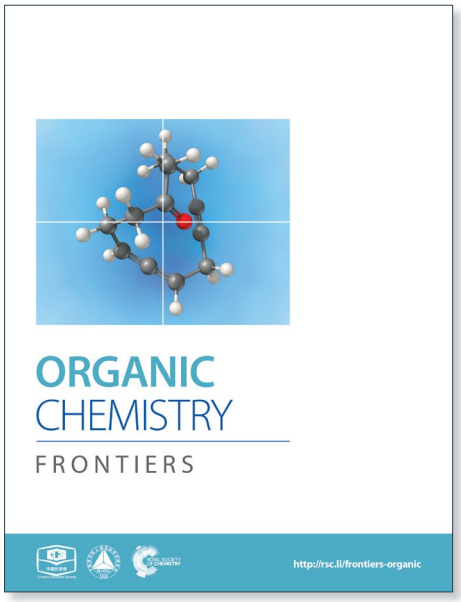

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ARTICLE

Access to Bicyclic Hydroxamate Macrocycles *Via* Intramolecular Aza-(4+3) Cycloaddition Reactions of Aza-Oxyallylic Cation Intermediates

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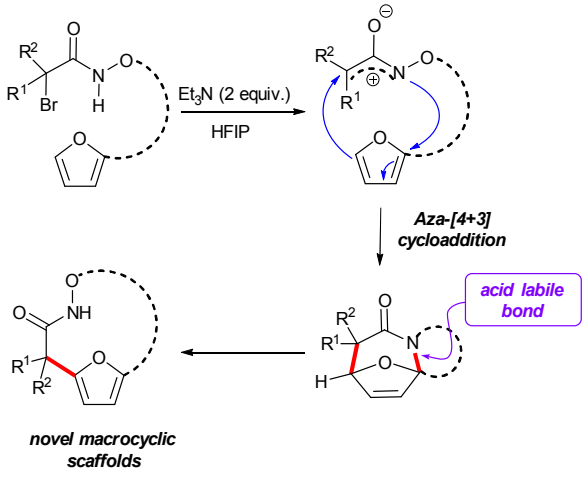
The intramolecular aza-(4+3) cycloaddition reactions of *in-situ* generated aza-oxyallylic cations and furans have been reported for the construction of medium sized hydroxamate macrocycles. This method provides direct access to 12-18 membered bicyclic macrocycles. The highly functionalized macrocycles have been transformed easily in to a wide range of highly functionalized heterocyclic scaffolds including lactones and lactams that could serve the synthesis of complex macrocyclic natural proudcts and pharmaceuticals

Macrocyclic motifs have demonstrated profound pharmacological properties. The balance between conformational flexibility and rigidity demonstrated by macrocyclic molecules often leads to specific and potent activity against a variety of biological targets.[1] Among the various classes of macrocycles, nitrogen-containing heterocycles have drawn considerable interest in chemical synthesis as they are widely represented in natural products and pharmaceuticals.

There are various methods reported for the construction of macrocycles. Lactonization and lactimization reactions are most commonly used methods.[2-6] Some other methods are cantered on constructing C-C bonds *via* nucleophilic substitution,[5] ring-closing metathesis[7-12] Pd-catalysed reactions,[13,14] Diels-Alder reactions,[3,15] cycloaddition reactions,[16,17] photochemical reactions,[18] among others. Aside from these approaches, multicomponent reactions have also been applied for the preparation of macrocyles.[19-23] Despite the promising biological activity of various macrocycles only a few reports have demonstrated the synthesis of five to eight membered cyclic hydroxamates from corresponding lactones.[24] We report herein, the development of a direct method of medium size hydroxamates using an aza-(4+3) cycloaddition reaction of furans and aza-oxyallylic cations. Additionally, we report further reactions of these highly functionalized macrocycles that provide access to products unique polycyclic architectures.

(4+3)-Cycloaddition reactions of oxyallyl cations have been reported as efficient methods to construct seven membered carbocycles and natural products.[25-28] As part of our interest in exploring the reactivity of electrophilic nitrogen species, we have reported the aza-(4+3) reaction of a transient aza- and diaza-oxyallylic cation and cyclic dienes to construct seven membered *N*-heterocycles.[29-32] Recently our group and Jimmy et. al. have reported (3+2) cycloaddition of aza-oxyallyl cationic intermediate to form pyrroloindolines.[33] In the course of studying the intramolecular cycloaddition reactions of α-halohydroxamates to afford tricyclic lactams, we observed further conversion of interesting macrocyclic products. We found that acid-catalyzed ring opening of polycyclic cycloadducts efficiently provided macrocyclic products *via* rupture of the aminal bond and rearomatization to the furan (Scheme 1).[31] These observations prompted us to further explore this strategy as a method for the construction of



Scheme 1 An aza-(4 + 3) cycloaddition of a stabilized aza-oxyallylic to form macrocyclic scaffolds.

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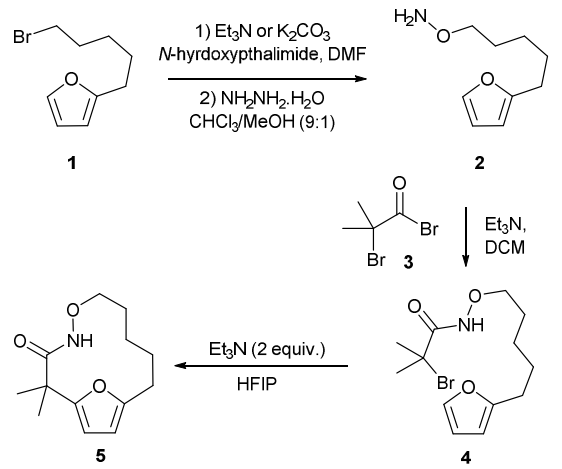
hydroxamate macrocycles. Herein, our efforts to expand the reactivity of *in-situ* generated aza-oxyallyl cationic intermediates by the dehydrohalogenation reaction of α-halohydroxamates to access medium rings bicyclic hydroxamates macrocycles are described.



Scheme 2 An intramolecular aza-[4 + 3] cycloaddition of a stabilized aza-oxyallylic with an appended furan to form 12 membered macrocycle.

Table 1 Optimization of the reaction condition for substrate **5**[a]

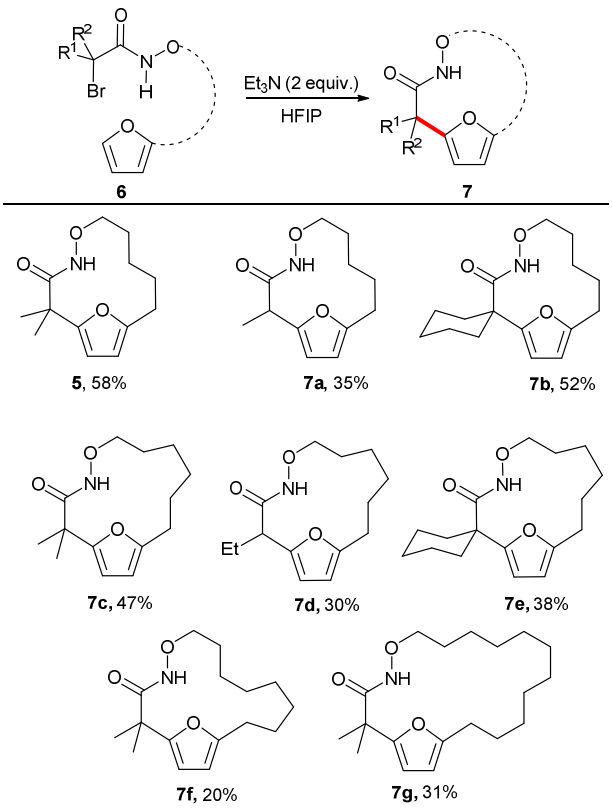
[a]All reactions were conducted by adding the base to a solution of the α-haloamide in HFIP and stirred until complete consumption of starting material. [b](M). [c]Isolated yield. [d]Refluxed. [e]Slow addition of TEA in HFIP over 2 h at room temperature. [f]Slow addition of SM in HFIP over 2 h at room temperature.

Entry	Base	Solvent	Conc.[b]	Time	Yield[c] (%)
1	TEA	TFE	0.25	0.5 h	15
2[d]	TEA, $LiClO_4$	Ether	0.25	3 h	NA
3	TEA	HFIP	0.25	1 h	36
4	DIPEA	HFIP	0.25	3 h	35
5	DBU	HFIP	0.25	0.5 h	50
6	TEA	HFIP	0.1	1 h	48
7	TEA	HFIP	0.05	2 h	45
8[e]	TEA	HFIP	0.1	2.5 h	58
9[f]	TEA	HFIP	0.1	2.5 h	36
10	Proton sponge	HFIP	0.25	3 h	47

Our studies began by preparing the hydroxylamine **2** in two steps from the 5-furylpentanyl bromide **1**. Acylation of the hydroxylamine with 2-bromo-2-methyl-propanoylbromide **3** provided the cycloaddition precursor **4**. Initial attempts to construct macrocycles *via* intramolecular (4+3)-cycloaddition reaction of *in-situ* generated aza-oxyallyl cation intermediate from halohydroxamates **4** using triethyl amine as a base and trifluoroethanol (TFE) as a solvent[34,35] exclusively provided solvolysis product of the α-halohydroxamate by TFE along with 15% desired macrocycle.[29] (Table 1, entry 1). Use of the more bulky and less nucleophilic solvent hexafluoroisopropanol (HFIP), found to be effective in suppressing solvolysis and increasing the yield of the macrocyclic product. Optimization of the reaction conditions were explored varying the concentration of α-halo-hydroxamate, the base and the order of addition. We found that slow addition of triethylamine to a solution of the halo-hydroxamate in HFIP (0.1 M) to be optimal reaction condition providing the desired macrocyclization product in 58% yield (Table 1, entry 8). The reaction conditions were further optimized by examination of the effects of temperature, solvent and catalyst loading, and the results are shown in Table 1.

With the optimal reaction conditions in hand, we explored the substrate scope for the synthesis of medium sized macrocycles (Table 2). In general all the reactions proceed smoothly to afford the desired product in satisfactory yield. Substitution at the 2-position the substrate were found to influence the overall rate of reaction, with tertiary halides undergoing the reaction at a faster rate than the corresponding secondary halides. It is hypothesized that tertiary carbon helps to stabilize the aza-oxyallyl cation as compared to secondary carbon, thereby accelerating the overall rate of the reaction.

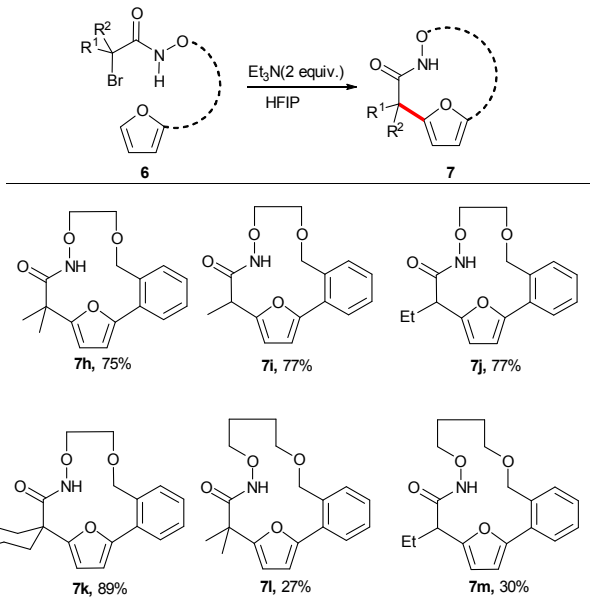
Table 2 Evaluation of the effect of variable tether length on macrocyclization reactions of α-halohydroxamates.[a]



[a]All reactions were conducted by adding the base to a solution of the α-haloamide in HFIP and stirred until complete consumption of starting material (See supporting information).

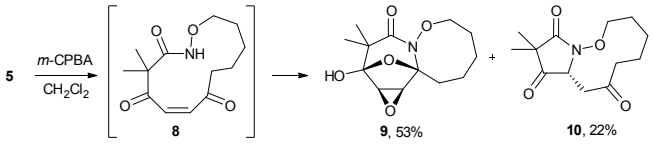
The unsubstituted α-halohydroxamate was found to be unreactive under the reaction conditions. The effect of tether length between both reacting termini was next explored. Increasing the tether length from five carbons to six carbons substantially diminished yield of desired products (**7c-e**) along with a complex mixture of side products. Extension of the tether further diminished the yield of the macrocyles, however still provided the large fifteen and eighteen membered macrocycles (**7f** and **7g**). We hypothesized that rigidifying the tether could enhance preference for cyclization by buttressing the reactive termini through the Thorpe-Ingold effect. To explore this hypothesis, substrates incorporating benzene within the tether were prepared and their macrocyclization under the optimal reaction conditions was explored. These substrates were found to be more effective than the less rigid precursors and provided desired macrocycle with good yield (**7h-j**). However, increasing tether length with the backbone again diminished the yield of desired macrocycles (**7k-m**).

Table 3 Evaluation of the effect of variable tether length having rigid backbone on macrocyclization reactions of α-halohydroxamates.[a]



[a]All reactions were conducted by adding the base to a solution of the α-haloamide in HFIP and stirred until complete consumption of starting material (See supporting information).

The highly functionalized macrocyclic products provide ample opportunity for the synthesis of biologically active macrocycles. The aromatic furan ring present in macrocycles **5,** underwent efficient oxidation with *m*-CPBA provides to afford epoxy lactam **9** as a major products and pyrrolidinedione **10**. The introduction of epoxy group in **9** and diketone group in **10** suggests that the reaction proceeds *via* ring opening of furan to provide diketone intermediate **8**, which was also observed in crude NMR analysis during the reaction. An OsO_4 oxidation of **5** provides the interesting bicyclic products **11** in good yield, now with the incorporation of a hydroxylated tetrahydrofuran ring. Friedel-Crafts acylation of the macrocyclic furan was found to be regioselective affording **12** and **13** in good yield.



Scheme 3 Oxidation of macrocycle **5** with *m*-CPBA

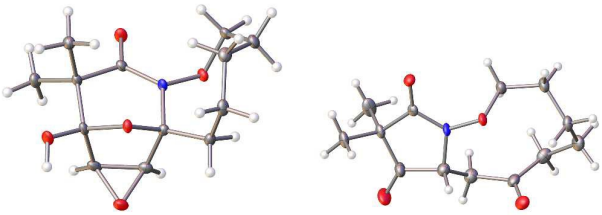
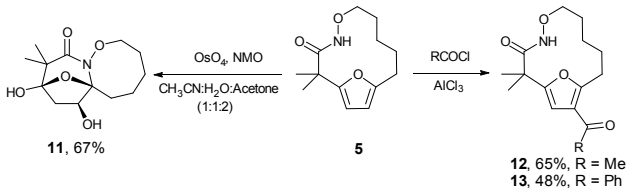


Figure 1 Thermal ellipsoid plot of **9** and **10** at 50% probability showing relative stereochemistry. Hydrogen atoms are represented as spheres of arbitrary radius. Grey = carbon, red = oxygen, blue = nitrogen.



Scheme 4 Osmium tetroxide oxidation and Fridel-Craft acylation of macrocycle **5**

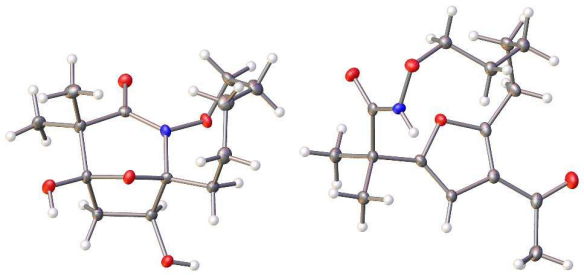
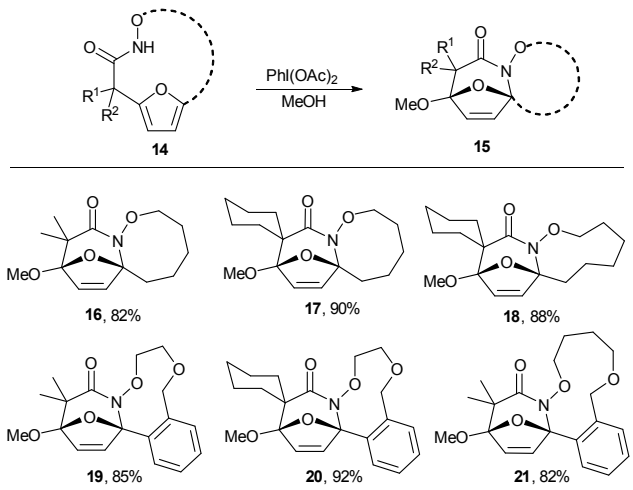


Figure 2 Thermal ellipsoid plot of **11** and **12** at 50% probability showing relative stereochemistry. Hydrogen atoms are represented as spheres of arbitrary radius. Grey = carbon, red = oxygen, blue = nitrogen.

N-acyl hydroxamates are established to be efficiently oxidized to electrophilic *N*-acyl nitrenium ions using hypervalent iodide oxidants. We envisioned that oxidation of the macrocyclic hydroxamates to the nitrenium ion would promote intramolecular electrophilic aromatic substitution by the pendant furan to form and oxidized tricyclic lactams. Treatment of the macrocyclic products **5** with $PhI(OAc)_2$ in methanol afforded tricyclic lactam **16** in good yield. We further explored this reactivity in other macrocycles **7b,e,h,k** and **7l**, which all provided desired tricyclic products in excellent yield

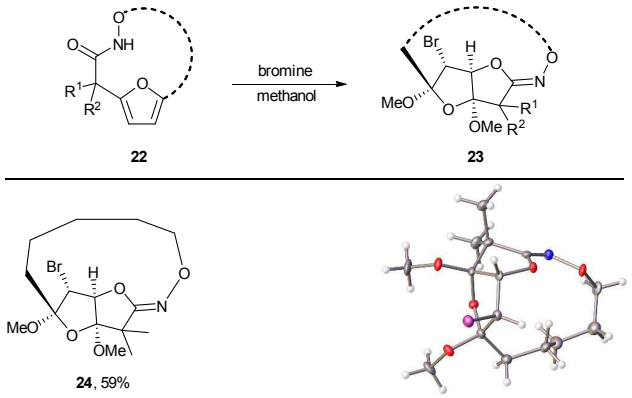
(Table 4). These orthogonal tricyclic lactams provide excellent opportunity for the construction of biologically active classes of heterocycles including nucleoside mimics and polyhydroxylated azepanes.

Table 4 Substrate scope for the oxidative lactamization of macrocycles[a]



[a]All reactions were conducted by adding $PhI(OAc)_2$ in to the solution of macrocycles in methanol.

Given the oxidative susceptibility of the furan ring, we pursued the bromination reaction of a few selected macrocycles (**5**, **7b**, **7c** and **7h**). Treatment of the macrocycles with bromine in methanol/ether provided the unique tricyclic imidate products (Figure 3) in good yield and as a single diastereoisomer. The stereochemistry of the product **24** was confirmed by X-ray crystallography. These highly functionalized products represent important building blocks that could be used to prepare a number of lactones natural products including ascorbigen,[36-38] microphynolides,[39] amarusine,[40] dichotomains,[41] helioscopin.[42]



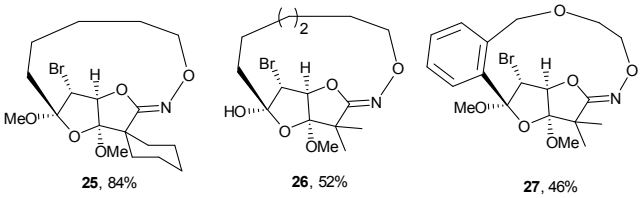


Figure 3 Bromination of macrocycles and thermal ellipsoid plot of **20** at 50% probability showing relative stereochemistry. Hydrogen atoms are represented as spheres of arbitrary radius. Grey = carbon, red = oxygen, blue = nitrogen, purple = bromine.

Conclusions

In summary, we have developed a novel macrocyclization method for the preparation of aza-macrocyclic compounds in fair to good yield. Intramolecular (4+3)-cycloaddition reactions of *in-situ* generated aza-oxyallylic cation intermediates followed by ring opening of bicyclic products provide medium sized macrocycles. The imbedded furan core undergoes a variety of different functionalization reactions, including regioselective Friedel-Crafts acylation/benzoylation, and a diversity of oxidative cyclizations using as *m*-CPBA, osmium tetroxide, $PhI(OAc)_2$ and Br_2/MeOH. These methods provide access to a wide range of biologically interesting architectures including polycyclic lactams, polyhydroxylated caprolactam, oxazines, and lactones. Further application of these strategies in total synthesis of the natural products is in under investigation in our group and will be reported in the future.

Crystal structure determination of compounds 9-12 and 20.

Crystal data for 9 (CCDC no. 1429958): $C_{13}H_{19}NO_5$, M = 269.29, monoclinic, a = 10.9816(5), b = 9.2222(4), c = 13.0751(6) Å, U = 1261.57(10) Å^3, T = 100.15 K, space group $P2_1/n$ (no. 14), Z = 4, 21 450 reflections measured, 2 898 unique (R_{int} = 0.0452) which were used in all calculations. The final $wR(F_2)$ was 0.1382 (all data).

Crystal data for 10 (CCDC no. 1429956): $C_{13}H_{19}NO_4$, M = 253.29, monoclinic, a = 11.3134(5), b = 9.4290(4), c = 12.7345(6) Å, U = 1268.29(10) Å^3, T = 100 K, space group $P2_1/n$ (no. 14), Z = 4, 21 397 reflections measured, 2 947 unique (R_{int} = 0.0433) which were used in all calculations. The final $wR(F_2)$ was 0.2774 (all data).

Crystal data for 11 (CCDC no. 1429955): $C_{14}H_{23}Cl_2NO_5$, M = 356.23, monoclinic, a = 11.7775(8), b = 8.7429(6), c = 16.8595(12) Å, U = 1670.0(2) Å^3, T = 100(2) K, space group $P2_1/n$ (no. 14), Z = 4, 23 957 reflections measured, 3 102 unique (R_{int} = 0.0652) which were used in all calculations. The final $wR(F_2)$ was 0.1240 (all data).

Crystal data for 12 (CCDC no. 1429957): $C_{15}H_{21}NO_4$, M = 558.65, monoclinic, a = 17.0197(5), b = 16.2710(5), c = 10.1414(3) Å, U = 2773.26(14) Å^3, T = 100 K, space group $P2_1/c$ (no. 14), Z = 4, 41 363 reflections measured, 5 170 unique (R_{int} = 0.0413) which were used in all calculations. The final $wR(F_2)$ was 0.1275 (all data).

Crystal data for 24 (CCDC no. 1429954): $C_{15}H_{24}BrNO_5$, M = 378.26, triclinic, a = 8.8508(8), b = 10.0352(8), c = 10.7879(9) Å, U = 811.83(12) Å^3, T = 99.65 K, space group P-1 (no. 2), Z = 2, 14 678 reflections measured, 3 029 unique (R_{int} = 0.0794) which were used in all calculations. The final $wR(F_2)$ was 0.0722 (all data).

Acknowledgements

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Notes and references

1 E. M. Driggers, S. P. Hale, J. Lee and N. K. Terrett, *Nat. Rev. Drug Discov*., 2008, **7**, 608.
2 A. Parenty, X. Moreau and J. M. Campagne, *Chem. Rev.,* 2006, **106**, 911.
3 X. F. Yu and D. Q. Sun, *Molecules*, 2013, **18**, 6230.
4 T. Gaich and P. S. Baran, *J. Org. Chem*., 2010, **75**, 4657.
5 V. M. Centelles, M. D. Pandey, M. I. Burguete and S. V. Luis, *Chem. Rev*., 2015, **115**, 8736.
6 W. A. Loughlin, J. D. A. Tyndall, M. P. Glenn and D. P. Fairlie, *Chem. Rev.,* 2004, **104**, 6085.
7 K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem. Int. Ed*., 2005, **44**, 4442.
8 C. Obradors, D. Leboeuf, J. Aydin and A. M. Echavarren, *Org. Lett.,* 2013, **15**, 1576.
9 J. Prunet, *Eu. J. Org. Chem*., 2011, 3634.
10 M. Ibrahim-Ouali, J. Zoubir and E. Romero, *Tetrahedron Lett.,* 2011, **52**, 7128.
11 M. Yu, C. B. Wang, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock and A. H. Hoveyda, *Nature*, 2011, **479**, 88.
12 V. M. Marx, M. B. Herbert, B. K. Keitz and R. H. Grubbs, *J. Am. Chem. Soc*., 2013, **135**, 94.
13 E. A. Crane and K. A. Scheidt, *Angew. Chem. Int. Ed.,* 2010, **49**, 8316.
14 S. P. Breazzano, Y. B. Poudel and D. L. Boger, *J. Am. Chem. Soc*., 2013, **135**, 1600.
15 C. W. Zapf, B. A. Harrison, C. Drahl and E. J. Sorensen, *Angew. Chem. Int. Ed.,* 2005, **44**, 6533.
16 D. E. Lonsdale and M. J. Monteiro, *J. Polym. Sci., Part A: Polym. Chem.,* 2010, **48**, 4496.
17 D. E. Lonsdale, C. A. Bell and M. J. Monteiro, *Macromolecules*, 2010, **43**, 3331.
18 K. Nishikawa, Y. Yoshimi, K. Maeda, T. Morita, I. Takahashi, T. Itou, S. Inagaki and M. Hatanaka, *J. Org. Chem.,* 2013, **78**, 582.
19 L. A. Wessjohann, D. G. Rivera and O. E. Vercillo, *Chem. Rev.,* 2009, **109**, 796.
20 L. A. Wessjohann and E. Ruijter, *Mol. Diversity*, 2005, **9**, 159.
21 D. G. Rivera and L. A. Wessjohann, *J. Am. Chem. Soc.,* 2009, **131**, 3721.
22 D. G. Rivera and L. A. Wessjohann, *J. Am. Chem. Soc*., 2006, **128**, 7122.
23 J. M. Knapp, J. C. Fettinger and M. J. Kurth, *Org. Lett.,* 2011, **13**, 4732.
24 S. Wolfe, M. C. Wilson, M. H. Cheng, G. V. Shustov and C. I. Akuche, *Can. J. Chem.,* 2003, **81**, 937.
25 J. Mann, *Tetrahedron*, 1986, **42**, 4611.
26 J. K. Cha and J. Oh, *Curr. Org. Chem.,* 1998, **2**, 217.
27 R. Noyori, S. Makino, T. Okita and Y. Hayakawa, *J. Org. Chem.,* 1975, **40**, 806.
28 H. M. Hoffmann, *Angew. Chem. Int. Ed.,* 1973, **12**, 819.
29 C. S. Jeffrey, K. L. Barnes, J. A. Eickhoff and C. R. Carson, *J. Am. Chem. Soc.*, 2011, **133**, 7688; K. L. Barnes, A. K. Koster and C. S. Jeffrey, *Tetrahedron Lett.*, 2014, **55**, 4690.
30 C. S. Jeffrey, D. Anumandla and C. R. Carson, *Org. Lett.*, 2012, **14**, 5764.
31 A. Acharya, J. A. Eickhoff and C. S. Jeffrey, *Synthesis*, 2013, **45**, 1825.
32 D. Anumandla, R. Littlefield and C. S. Jeffrey, *Org. Lett.*, 2014, **16**, 5112.
33 (a) A Acharya, D Anumandla, C. S Jeffrey, *J. Am. Chem. Soc.*, 2015, **137**, 14858; (b) M. C. DiPoto, R. P. Hughes, and J. Wu, *J. Am. Chem. Soc.*, 2015, **137**, 14861.
34 B. Föhlisch, E. Gehrlach and R. Herter, *Angew. Chem. Int. Ed.*, 1982, **21**, 137.
35 R. Herter and B. Föhlisch, *Synthesis*, 1982, 976.
36 A. Tai, K. Fukunaga, A. Ohno and H. Ito, *Biosci. Biotech. Bioch.*, 2014, **78**, 1723.
37 M. Opietnik, S. N. B. S. Jaafar, M. Becker, S. Boehmdorfer, A. Hofinger and T. Rosenau, *Mini-Rev. Org. Chem.*, 2012, **9**, 411-417.
38 C. H. Wang, H. S. Huang, N. T. Dai, M. J. Sheu and D. M. Chang, *Phytother. Res.*, 2013, **27**, 1863.
39 H. Ghanem, H. Haba, L. Marcourt, M. Benkhaled and J. L. Wolfender, *Nat. Prod. Res.*, 2014, **28**, 1800.
40 J. Sun, P. Zhang, Q. Wei, H. Xun, F. Tang, Y. Yue, L. Li, X. Guo and R. Zhang, *Tetrahedron Lett.*, 2014, **55**, 4529.
41 X. L. Li, X. Cheng, L. M. Yang, R. R. Wang, Y. T. Zheng, W. L. Xiao, Y. Zhao, G. Xu, Y. Lu, Y. Chang, Q. T. Zheng, Q. S. Zhao and H. D. Sun, *Org. Lett.*, 2006, **8**, 1937.
42 S. H. Lee, M. Jun, J. Y. Choi, E. J. Yang, J. M. Hur, K. Bae, Y. H. Seong, T. L. Huh and K. S. Song, *Arch. Pharm. Res.*, 2007, **30**, 827.