Synthetic Approach to Oxyfunctionalized Polycycles via Application of Ring-Rearrangement Metathesis as a key step

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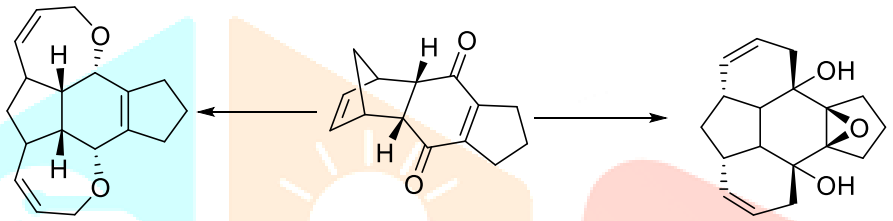
Abstract

Ring-Rearrangement metathesis (RRM) is used as key step for the synthesis of oxyfunctionalised carbocyclic compound such as oxacyclic derivatives, oxa-bowl and highly functionalized spiro derivatives. This methodology easy, cheap and useful protocol for the synthesis of Oxacycles and Polycycles synthesis.



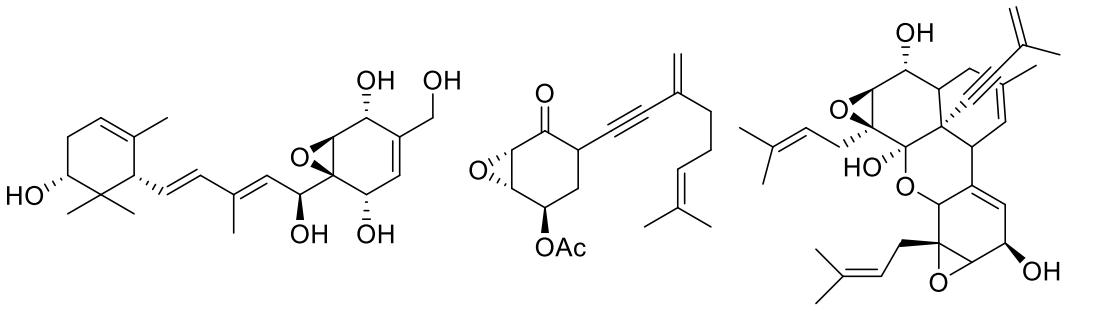
Scheme

Keywords: Ring-Rearrangement Metathesis (RRM), Diels-Alder, Polycycles, Oxacycles etc.

Introduction

Ring-rearrangement metathesis (RRM) is an intramolecular ring-opening/ring-closing domino process in which a carbocycles may get transformed into heterocycles and vice-versa. In this process the stereochemical information is transferred from reactant to product. The strained cyclic olefins undergo metathetic ring-opening under the influence of Grubbs catalyst to produce open chain alkene molecules.[1] Diels−Alder (DA) reaction is an important tool for the construction of several norbornene derivatives which serves as a suitable precursor in metathetic transformations.[2] Herein, we report highly condensed carbocyclic system bearing epoxide ring and hydroxy group functionalization. There are several biologically active natural products containing epoxide ring such as those encountered in epoxyquinone and they exhibit phytotoxicity, antibacterial and antifungal properties.[3] In our current methodology we designed epoxyquinone type ring system which underwent further transformation to produce condensed polycycles. We have also constructed the spirocyclic core containing polycycles and such spiro rings constitutes the structural motifs of various natural and non-natural products including medicinally important molecules.[4]

Figure 1. Epoxyquinone based monoterpenoid natural products



Anthrosporol B Tricholomenyn A Dimericbiscognienyne A

Figure 1.

Reterosynthetic perspective towards carbocycles and oxacycles is depicted in figure 2. The pentacycles **3** and spirocycles **4** was accessed from DA adduct **1** and **2** respectively via Grignard reaction, epoxidation and RRM. Oxa-bowl **5** and **6** could be obtained through reduction and RRM approach.

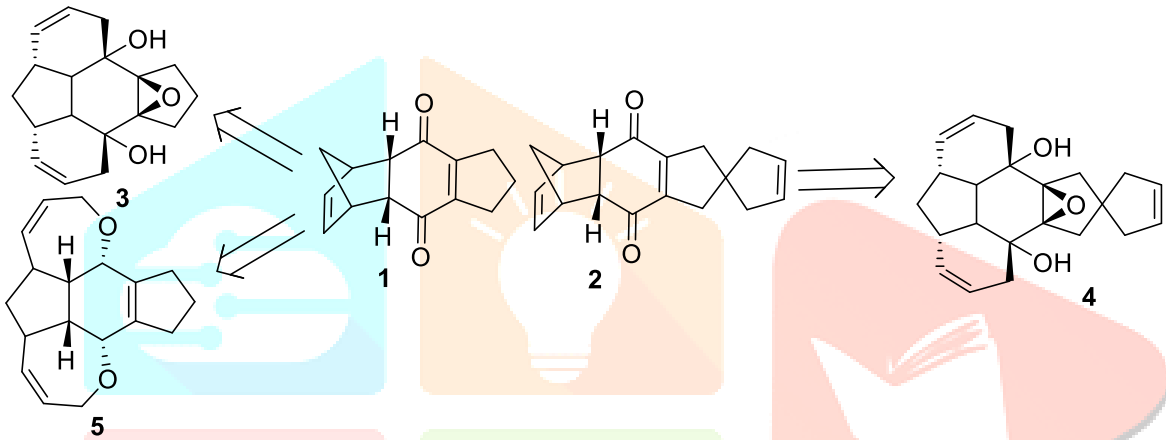


Figure 2. Reterosynthetic Analysis

Results and Discussion

Taking the advantage of our previously developed strategy, norbornene system was produced via DA reaction between cyclopentadiene and benzoquinone derivative.[5] Our strategy began with the preparation of indane benzoquinone which is a suitable precursor in DA reaction as already reported by our group.[6] Thus norbornene derivative **1** obtained via DA reaction between easily accessible cyclopentadiene and **13** underwent Grignard reaction to produce diallylated derivative **14** which was sought to be reactive towards RRM. But unfortunately, **14** upon subjected to metathetic condition underwent decomposition (Scheme 1). It was anticipated that six-membered ring containing double bond might be participating in some rearrangement process and thus inhibiting the metathesis sequence to take place. With this hypothesis in mind, ring double bond was reduced using Zn-AcOH which ultimately leads to the complex mixture of diatereomers.

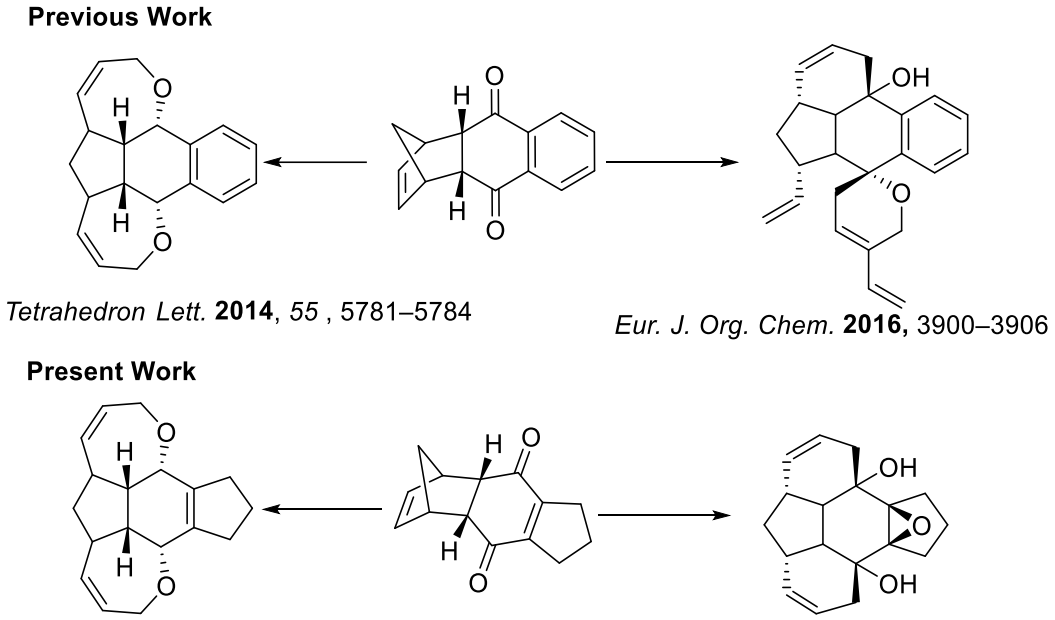
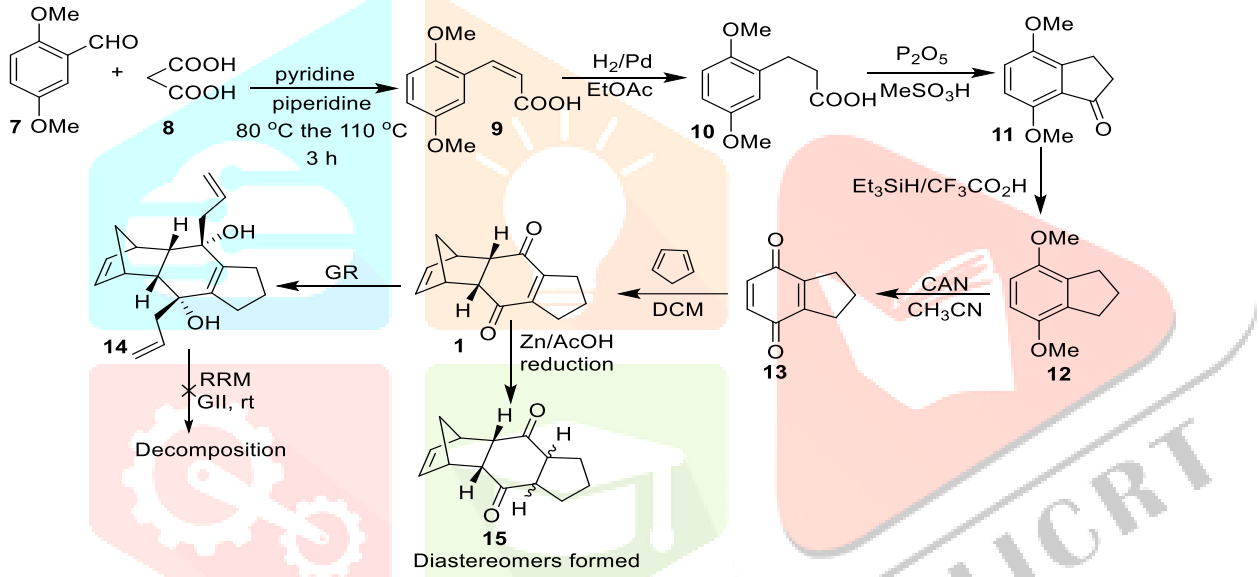
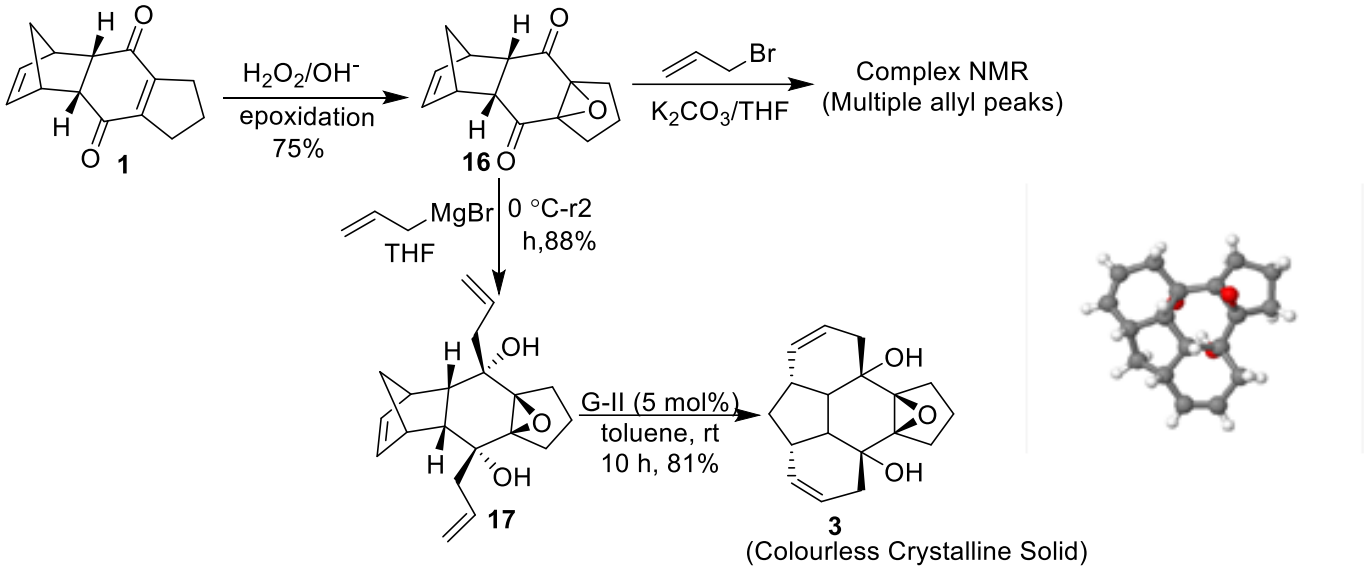


Figure 3.



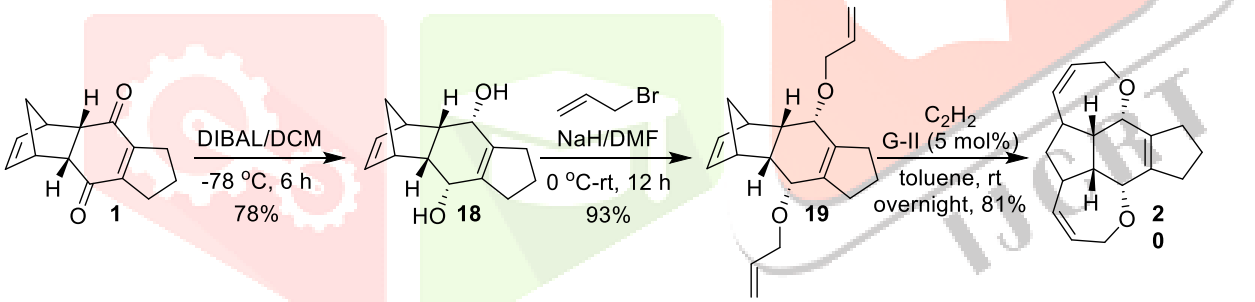
Scheme 1. Attempted Synthesis of Carbocyclic compound *via* RRM.

After getting unsuccessful results as illustrated in scheme 1, we envisioned an alternative method for the removal of double bond which involves its conversion into the epoxide ring. To begin with, the DA adduct **1** was treated with H_2O_2 under basic condition to deliver the keto-epoxide 16 which was treated with allyl magnesium bromide at rt for 3 h produced diallylated tertiary alcohol **17** in good yield (87%). RRM of **17** went smoothly with G-II (5 mol%) catalyst under rt condition to afford highly condensed ring-rearranged pentacyclic system **3** in 72% yield as a crystalline compound. The stereochemistry of **17** was unambiguously confirmed by XRD study.



Scheme 2. Synthesis of highly functionalized hexacyclic compound *via* RRM approach

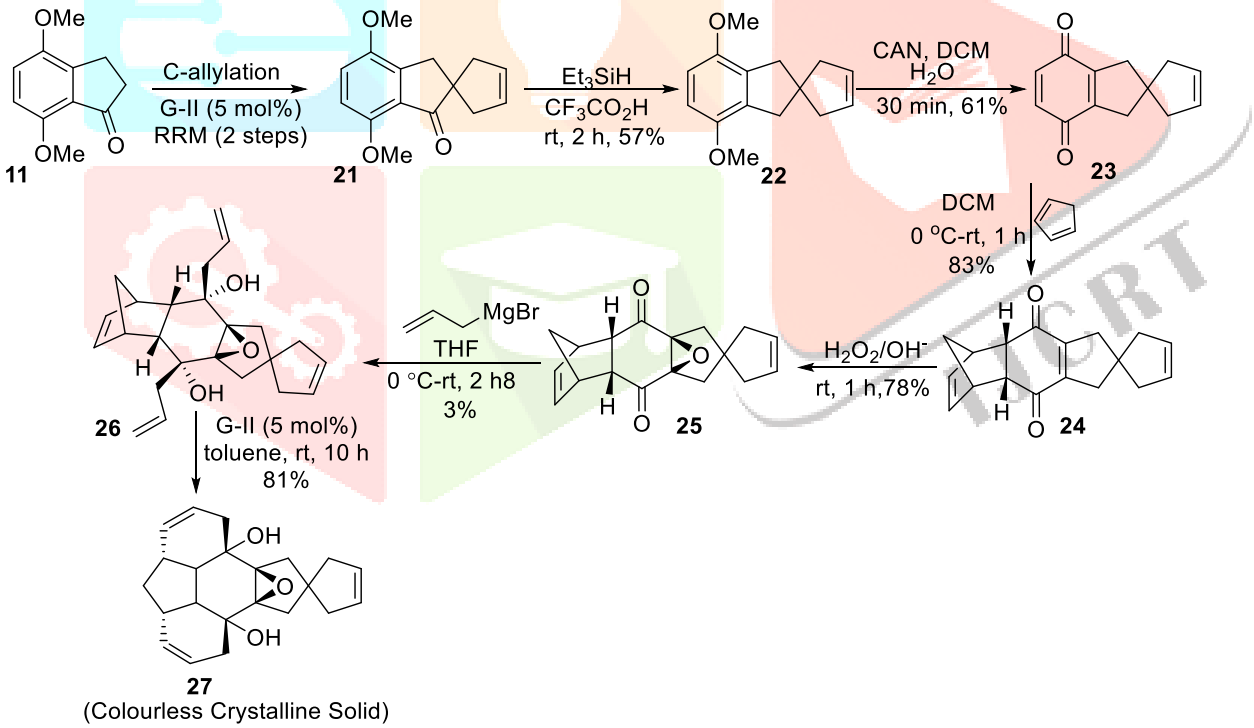
Alongwith similar lines, when epoxide **16** upon subjecting to *C*-allylation in the presence of mild base K_2CO_3 in order to get *C*-allylated compound which could produce propellane or some ring-rearranged skeleton, however we failed in our attempt as complex NMR showing multiple allyl peak was observed (Scheme 2). We next aimed to synthesize oxa-bowl system **20** derived from DA adduct **1** which was accomplished by DIBAl reduction of **1** to deliver the diol **18** followed by its *O*-allylation. The *O*-allylated derivative **19** serves as a suitable precursor of RRM and thus upon subjecting to metathetic condition using G-II catalyst leads to the formation of oxacyclic compound **5** in good yield (Scheme 3).



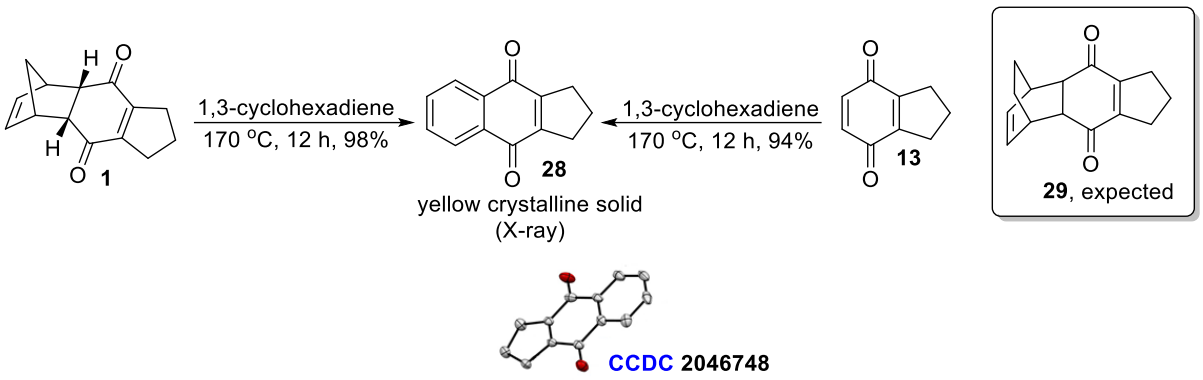
Scheme 3. Synthesis of oxacyclic derivative *via* RRM

Next, we decided to extend our strategy into the spirocyclic system and for this purpose the DA adduct **2** was synthesized using dimethoxy spiroketone as a starting material. Similar to our previous synthetic approach the keto group in **21** was converted into methylene group using triethylsilane and trifloroacetic acid (TFA) in DCM to give **22** in 57% yield. Next CAN oxidation of **22** followed by DA reaction of the crude mixture **23** with freshly ditilled cyclopentadiene produced the orange coloured solid spiro adduct **24** in 83% yield. Based on previous results, here also the ring double bond was converted into epoxide **25** and then subjected to Grignard reaction condition to deliver the Grignard addition product **26** in good yield (83%). Finally, **26** underwent RRM in the presence of G-II catalyst a rt furnished the hexacyclic spiro derivative with highly fused ring system **27**.

Encouraged by our successful results we planned to investigate the metathetic behviour of bicyclo [2.2.2] octene system which could be obtained by DA reaction between 1,3-cyclohexadiene and benzoquinone derivative **13** at high temperature of 170 ℃ in a sealed tube for 24 h (Scheme 5). To our surprise instead of getting the expected DA adduct **29**, the aromatized product ie., naphthoquinone ring moiety was achieved in excellent yield (86%) as a yellow crystalline solid. Same result was observed when the DA adduct **1** was heated in a sealed tube with cyclohexadiene at 170 ℃. The structure of the product was confirmed by single crystal X-ray diffraction analysis as well as NMR spectroscopy. Upon literature survey and our own understanding, we hypothesized that initially the [4+2] cycloaddition reaction happened, but at high temperature the cycloadduct undergone the cycloreversion (retro-DA reaction) resulting in the elimination of volatile ethylene molecule and underwent aromatization sequence. The compound was recrystallized by petroleum ether and ethyl acetate (4:1) in the refrigerator by slow evaporation of solvent. To our pleasure, the obtained system contains naphthoquinone ring which represents the basic core ring system of vitamin K.[7a] Notably, naphthoquinone ring containing compounds are known to be the major component of biologically important molecules like griffithazanone A exhibit antitumor activity against human cancer cell lines as well as shows antibacterial activity.[7b] Also, quinone ring system is found in several other natural products possessing antimalarial and antiarboviral activity.[7c]

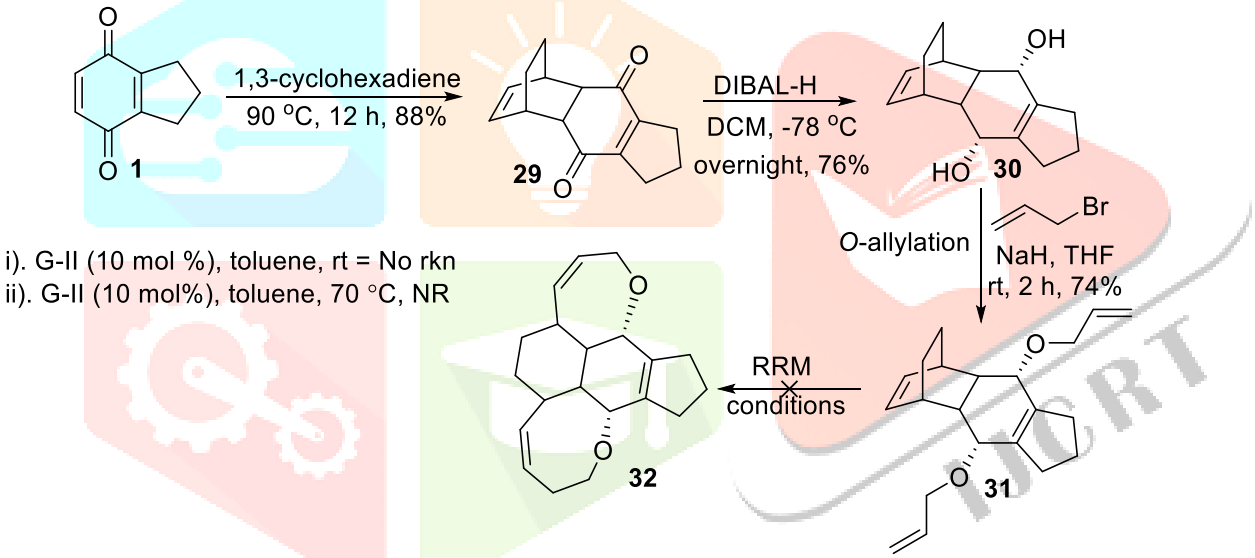


Scheme 4. Synthesis of highly functionalized spiro derivative via RRM approach.



Scheme 5 Synthesis of Naphthoquinone via Diels−Alder / Retro Diels−alder reaction

It was interesting to note that when the same reaction mixture was heated at less temperature ie., at 90 °C smoothly delivers the desired DA cycloadduct **29** containing bicyclo [2.2.2] octene ring system in 88% yield. Initially we chose to design oxacyclic derivative, therefore DIBAL reduction of **29** followed by its *O*-allylation produced *O*-allylated derivative **31** (74%), which was found to be unreactive towards metathetic catalysts which may be due to less strain associated with bicyclic ring system.



Scheme 6. Attempted synthesis of Oxa-bowl **32** via RRM Approach

Conclusion

In conclusion, we have successfully executed RRM strategy to design various polycycles and oxacycles using simple reactions like epoxidation and Grignard reactions in the intermediate steps.

Interpretation of spectra

1) **MF: $C_{14}H_{14}O_2$(1)**
   H^1 NMR (δ scale, 400Hz, $CDCl_3$): 2.30(t, 2H, J=7.2), 2.64(d,1H, J=10.2), 2.64(d, 1H, J= 10.2), 1.85(t,2H, J=7.2), 2.30(t, 2H, J=7.2), 3.30(dd, 1H), 2.30(t, 2H, J=7.2), 3.30(dd, 1H), 6.25(dd, 1H, J=10.3), 6.25(dd, 1H, J=10.3), C^{13}NMR (400Hz, $CDCl_3$): 12.4, 35.6, 48.0, 48.6, 49.7, 136.1, 152.9, 198.7
2) **MF: $C_{18}H_{22}O_3$ (3)**
   H^1 NMR (δ scale, 400Hz, $CDCl_3$): 6.30(d,1H, J=10.9 & 6.4), 5.68(d,1H, J= 10.9 & 6.4), 1.64(q, 1H),1.39(q, 1H), 2.09(1H), 1.17(q,1H, J=7), 2.17(q,1H, J=7), 1.94(1H), 5.09(1H), 1.63(q,1H), 1.53(q,1H), 1.73(d,1H), 1.53(d,1H), C^{13}NMR (400Hz, $CDCl_3$): 20.4, 26.7, 36.2, 36.8, 40.6, 44.5, 72.0, 77.0, 126.0, 133.2.

3) MF: $C_{14}H_{16}O_2$(15)

H^1 NMR (δ scale, 400Hz, $CDCl_3$): 6.25(dd, 1H, J=10.3), 6.25(dd, 1H, J=10.3), 2.62(m, 1H), 0.94(m, 1H), 0.69(m, 1H), 2.26(m, 1H), 1.79(q, 2H, J=7.2), 1.90(q, 2H, J=7.2), 2.65(q, 1H). C^{13}NMR (400Hz, $CDCl_3$):23.0, 23.8, 46.6, 47.8, 48.0, 52.7, 135.9, 212.4.

4) MF: $C_{20}H_{26}O_2$(14)

H^1 NMR (δ scale, 400Hz, $CDCl_3$): 6.25(dd, 1H, J=10.3), 6.25(dd, 1H, J=10.3), 5.15(dd, 1H, J=2.1, J=17), 4.95(dd, 1H, J=2.1, J=17), 5.92(dd, 1H, J=2.1, J=17), 4.82(s, 1H), 2.62(m, 1H), 0.94(m, 1H), 0.69(m, 1H), 2.26(m, 1H), 2.32(t, 2H, J=7.2), 1.90(q, 2H, J=7.2). C^{13}NMR (400Hz, $CDCl_3$): 23.0, 27.0, 37.4, 40.0, 48.1, 49.3, 75.5, 119.8, 134.1, 147.3, 135.9.

5) MF: $C_{14}H_{14}O_3$(16)

H^1 NMR (δ scale, 400Hz, $CDCl_3$): 1.73(t, 1H, J=7.2), 1.63(t,1H, J=7.2), 2.64(d,1H, J=10.2), 2.64(d, 1H, J= 10.2), 1.93(t,1H, J=7.2), 1.83(t,1H, J=7.2), 1.75(t, 1H), 1.50(t, 1H), 3.30(dd, 1H), 3.30(dd, 1H), 6.25(dd, 1H, J=10.3), 6.25(dd, 1H, J=10.3), C^{13}NMR (400Hz, $CDCl_3$): 12.8, 35.8, 48.0, 48.6, 49.7, 78.10, 152.7, 198.9.

6) MF: $C_{20}H_{26}O_3$(17)

H^1 NMR (δ scale, 400Hz, $CDCl_3$): 6.25(dd, 1H, J=10.3), 6.25(dd, 1H, J=10.3), 5.15(dd, 1H, J=2.1, J=17), 4.95(dd, 1H, J=2.1, J=17), 5.92(dd, 1H, J=2.1, J=17), 4.82(s, 1H), 2.62(m, 1H), 0.94(m, 1H), 0.69(m, 1H), 2.26(m, 1H), 1.65(t, 1H, J=7.2), 1.55(t, 1H, J=7.2), 1.74(q, 1H, J=7.2), 1.64(q, 1H, J=7.2). C^{13}NMR (400Hz, $CDCl_3$): 23.0, 27.0, 37.4, 40.0, 48.1, 49.3, 75.5, 119.8, 134.1, 78.6, 135.9.

7) MF: $C_{22}H_{26}O_3$(27)

H^1 NMR (δ scale, 400Hz, $CDCl_3$): 6.30(d,1H, J=10.9 & 6.4), 5.68(d,1H, J= 10.9 & 6.4), 1.64(q, 1H),1.39(q, 1H), 2.09(1H), 1.17(q,1H, J=7), 2.17(q,1H, J=7), 1.94(1H), 5.09(1H), 1.63(q,1H), 1.53(q,1H), 1.73(d,1H), 1.53(d,1H), 2.46(t, 2H J=2.3), 5.61(q, 1H, J= 16.4), C^{13}NMR (400Hz, $CDCl_3$): 20.4, 26.7, 36.2, 36.8, 40.6, 44.5, 72.0, 77.0, 126.0, 133.2.

8) MF: $C_{18}H_{26}O_2$(20)

H^1 NMR (δ scale, 400Hz, $CDCl_3$): 1.64(q, 1H), 1.39(q, 1H), 2.09(m, 1H), 5.68(t, 1H, J=16.1), 5.61(q, 1H J=16.1), 4.09(dd, 1H), 3.99(dd,1H), 3.66(t. 1H), 2.28(t, 2H) 1.90(q, 2H). C^{13}NMR (400Hz, $CDCl_3$): 22.4, 29.1, 34.4, 36.9, 40.7, 68.7, 80.0, 129.8, 135.8, 137.6.

9) MF: $C_{13}H_{10}O_2$(28)

H^1 NMR (δ scale, 400Hz, $CDCl_3$): 1.88(q, 2H), 2.32(t, 2H), 7.60(d, 1H), 7.72(t, 1H). C^{13}NMR (400Hz, $CDCl_3$): 12.5, 35.5, 126.8, 131.8, 135.0, 147.2, 183.0. ss

10) MF: $C_{21}H_{26}O_2$(31)

H^1 NMR (δ scale, 400Hz, $CDCl_3$): 6.25(dd, 1H, J=10.3), 6.25(dd, 1H, J=10.3), 5.15(dd, 1H, J=2.1, J=17), 4.95(dd, 1H, J=2.1, J=17), 5.92(dd, 1H, J=2.1, J=17), 2.62(m, 1H), 1.49(t, 1H), 1.24(t, 1H), 2.26(m, 1H), 2.32(t, 2H, J=7.2), 1.90(q, 2H, J=7.2), 3.66(d, 2H, J=2.1). C^{13}NMR (400Hz, $CDCl_3$): 23.0, 27.0, 37.4, 40.0, 48.1, 49.3, 75.5, 119.8, 134.1, 147.3, 135.9.

References:

1. Ling, R.; Yoshida, M.; Mariano, P. S. *J. Org. Chem.* **1996**, *61*, 4439–4449.
2. Goering, B. K. Ph.D. Dissertation, Cornell University, 1995.
3. Haslam, E. *Shikimic Acid Metabolism and Metabolites*, John Wiley & Sons: New York, 1993.
4. Buchanan, J. G.; Sable, H. Z. In *Selective Organic Transformations*; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1972; Vol. 2, pp 1–95.
5. Lyle, F. R. U.S. Patent 5 973 257, 1985; *Chem. Abstr.* **1985**, *65*, 2870.
6. (a) Du L., Risinger A. L., Yee S. S., Ola A. R. B., Zammiello C. L., Cichewicz R. H., Mooberry S. L. J. Nat. Prod. 2019, 82, 583. (b) Danielsson, J., Sun, D. X., Chen, X–Y., Risinger, A. L., Mooberry, S. L., Sorensen, E. J. Org. Lett. 2017, 19, 4892.
7. (a) Eaton, P. E., Sidhu, R. S., Langford, G. E., Cullison, D. A., Pietruszewski, C. L. *Tetrahedron* 1981, *37*, 4479.
   (b) Mehta, G. Yaragorla, S. *Tetrahedron Lett.* 2011, *52*, 4485. (c) Mehta, G. Reddy, K. S. *Tetrahedron Lett.* 1996, *37*, 2289.