

# Synthesis of $\alpha$ -Onoceradiene-like Terpene Dimers by Intermolecular Metathesis Processes

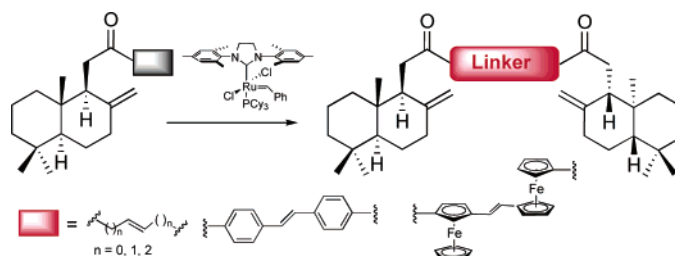
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## ABSTRACT



New  $\alpha$ -onoceradiene analogues having a terpene homodimer skeleton are accessible from Weinreb's amide 2 derived from commercial (*R*)-(+)-sclareolide using an intermolecular metathesis reaction as the key step to build the linker joining both terpene moieties.

Natural products chemistry has provided a superb variety of compounds having very diverse structures and biological activities.<sup>1</sup> However, there is an increasing awareness of the usefulness of accessing new natural product based structures, without relying on their serendipitous isolation from natural sources. Recent trends in natural products chemistry follow two parallel pathways: the preparation of hybrid<sup>2</sup> compounds which combine at least two structural features derived from different natural products and the incorporation of natural products into organometallic complexes leading to new entities.<sup>3</sup> In fact, developing versatile methods for the preparation of hybrid or bioorganometallic natural products

opens doors to an inextinguishable and structurally diverse variety of small molecules available for testing. However, to succeed in implementing these ideas, a deeper knowledge regarding how densely functionalized molecules behave toward simple organic or organometallic reagents is required.<sup>4</sup>

During the last years, symmetric molecules derived from the joining of two identical moieties have slowly gained importance as ligands for proteins.<sup>5</sup> Dimers may activate cellular processes<sup>6</sup> or may increase the affinity of ligands to their binding sites by providing an extra anchoring domain.<sup>7</sup> For example, a number of glycopeptides form dimers and their tendency to dimerize has been correlated to their

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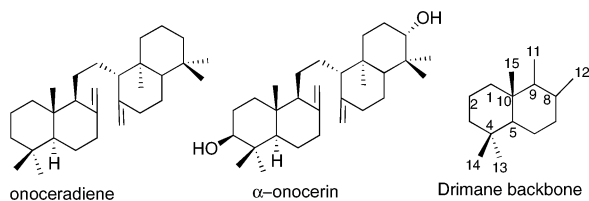
(5) Clemons, P. A. *Curr. Opin. Chem. Biol.* **1999**, 3, 112.

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biological activities.<sup>8</sup> Furthermore, dimeric and oligomeric steroids have shown a wide variety of different properties, including micellar and liquid crystal behavior, and some of them are cytotoxins.<sup>9</sup>

During our work directed toward the preparation of structurally diverse natural products and natural product hybrids,<sup>10</sup> which are capable of invoking a broad spectrum of biological activities, we devised a simple route to prepare a series of onocerane-like derivatives. Onoceranes (Figure 1) constitute a reduced family of triterpenes isolated, among

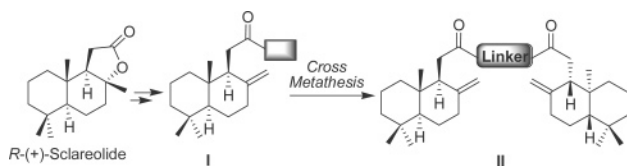


**Figure 1.**

others, from plants belonging to *Lycopodium* genus.<sup>11</sup>

Apart from their role in organic geochemistry, as terrestrial biomarkers for detecting paleoenvironmental changes,<sup>12</sup> some onoceranoids,<sup>13</sup> like  $\alpha$ -onocerin, have been found to inhibit acetylcholinesterase activity,<sup>14</sup> having therapeutic potential in the treatment of Alzheimer's disease. From a structural point of view, the onocerane backbone may be considered as a dimer, since it has two identical parts containing 15 carbon atoms each, having a drimane skeleton. Therefore, access to onocerane analogues possessing diverse tethers joining the C15 moieties may be gained by using a cross-metathesis reaction.<sup>15</sup> In this paper, an approach to onoceradiene-like derivatives by self-cross-metathesis, following the approach depicted in Scheme 1, is reported.

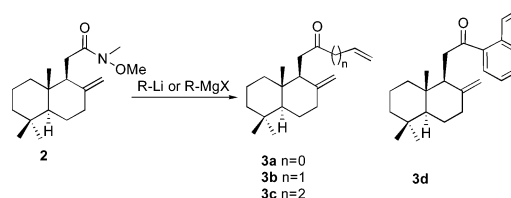
**Scheme 1**



Ketones **3** were prepared from Weinreb's amide **2** obtained from (*R*)-(+)-sclareolide **1**<sup>16</sup> according to the procedure previously described by us.<sup>16b</sup> Ketones **3a** and **3b** were

prepared in quantitative yields by reaction with the corresponding chloro or bromo Grignard reagents, while ketones **3c** and **3d** were obtained by addition of the lithium reagents obtained in situ from 4-bromo-1-butene and 2-bromostyrene respectively, to amide **2** (Scheme 2).

**Scheme 2**



Compounds **3b** and **3c** were reacted with first-generation Grubbs' catalyst **4a** in boiling  $\text{Cl}_2\text{CH}_2$ . Dimers **5b** and **5c** were obtained in variable yields, using high loads (up to 20%) of catalyst, as *E/Z* isomeric mixtures. The presence of intramolecular tricyclic derivatives arising from the metathesis of the  $\Delta^{8(12)}$  exocyclic double bond and the side-chain double bond was not observed.<sup>17</sup>

The reaction of commercial second-generation Grubbs' catalyst **4b**, in boiling  $\text{Cl}_2\text{CH}_2$ , with compounds **3b** and **3c** produced dimers **5b** and **5c** in 37% and 76% yields, respectively.<sup>18</sup> Compounds **5b** and **5c** were obtained as 5:1 *E/Z* mixtures of isomers in both cases at the new double bond.<sup>19</sup> Assignment of  $^1\text{H}$  and  $^{13}\text{C}$  NMR data was made by extensive 2D-NMR analysis. Comparison of the  $^{13}\text{C}$  chemical shifts of the newly formed olefinic and allylic carbons allowed assignment of each isomer.<sup>20</sup> Thus, for isomer **5bE**, the aforementioned carbons resonate at 126.5 and 46.4 ppm, respectively, while the same carbons for the *Z* isomer appear at higher field (124.8 and 41.7 ppm, respectively). The same analysis was made for dimer **5c**. Additionally, compound **3b** yielded, together with dimer **5b**, the  $\alpha,\beta$ -unsaturated

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(13)  $\beta$ -Onocerin and  $\beta$ -onoceradiene have been recently synthesized by Barrero and co-workers; see: Barrero, A. F.; Herrador, M. M.; Quílez del Moral, J. F.; Arteaga, P.; Arteaga, J. F.; Piedra, M.; Sánchez, E. M. *Org. Lett.* **2005**, *7*, 2301. (+)- $\alpha$ -Onocerin has been synthesized by Corey and co-workers; see: Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290.

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(15) Despite the explosive growth of the use of metathesis in organic and organometallic chemistry, its use in the preparation of homodimers derived from natural products has been restricted to a synthesis of a FK506 dimer (FK1012); see ref 6. While this manuscript was being prepared, the synthesis of new artemisinin-derived dimers by self-cross-metathesis was reported; see: Grellepois, F.; Crousse, B.; Bonnet-Delpon, D.; Bégue, J. P. *Org. Lett.* **2005**, *7*, 5219.

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(17) The drimane sesquiterpenoid systematic numbering has been adopted for the decalin framework of the compounds synthesized in this paper. See: Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman and Hall: London, 1991; Vol. 1.

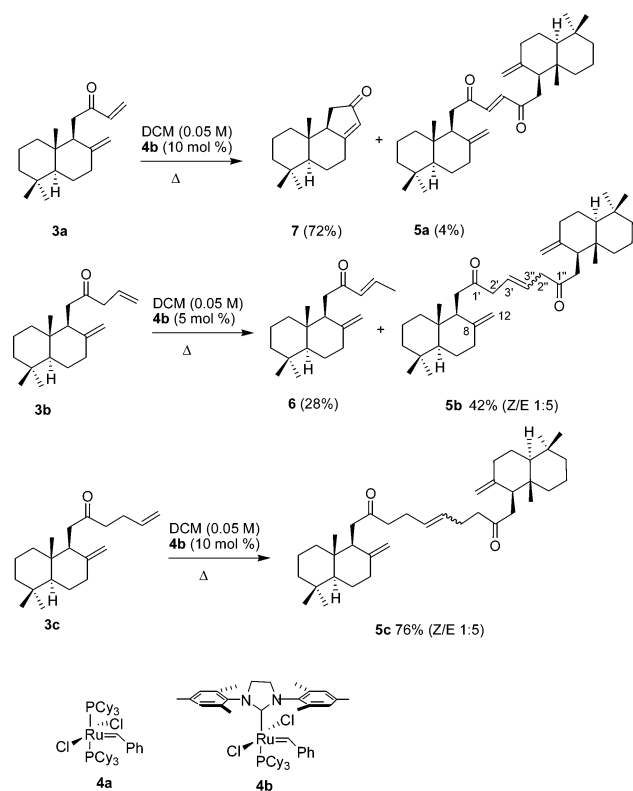
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(10) (a) de la Torre, M. C.; García, I.; Sierra, M. A. *Chem. Eur. J.* **2005**, *11*, 3659. (b) Alvaro, E.; de la Torre, M. C.; Sierra, M. A. *Org. Lett.* **2003**, *5*, 2381.

ketone **6** in 28% yield. Compound **6** is the sole reaction product (92% isolated yield) when the reaction of **3b** is carried out in refluxing toluene using the same catalyst.<sup>21</sup> The  $\alpha,\beta$ -unsaturated ketone **3a** failed to give dimer **5a** in acceptable yields (4%). In fact, the tricyclic ketone **7** was the main reaction product (72% yield) in this case. Tricyclic ketone **7** was formed by the RCM reaction of **3a**. Minute amounts of ketone **7**, which has a weak woody odor, have been isolated from the mixture of products obtained in the treatment of (*R*)-(+)-sclareolide with Eaton's reagent (Scheme 3).<sup>22</sup> Finally, alkene **3d** did not produce the desired ho-

Scheme 3



modimer. Unreacted starting material was recovered in all reaction conditions tested.

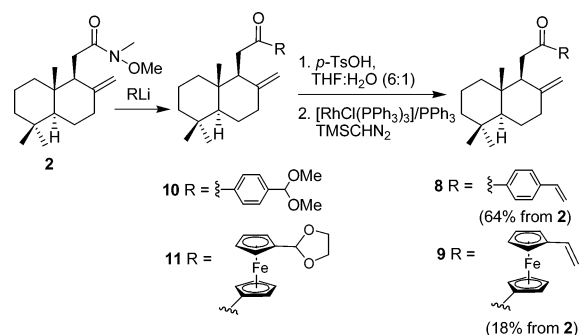
The direct addition of 4-lithiostyrene or lithium vinylferrocene to Weinreb's amide **2** gave the desired ketones **8** and

(18) The following procedure for the metathesis of compound **3b** is representative for the reactions of compounds **3a** and **3c**: To a previously degassed DCM (8.8 mL) solution (0.05 M) of the ketone **3b** (120 mg, 0.44 mmol) was added the catalyst **4b** (19 mg, 0.02 mmol, 5%). The flask was fitted with a condenser and refluxed for 6 h. The reaction mixture was then reduced in volume to 0.5 mL and purified by silica gel chromatography (hexanes/AcOEt ranging from 100:0 to 95:5) to give pure **6** (34 mg, 28%) as a clear oil and **5b** (42 mg, 37%, *E/Z* ratio 5:1). Data for **5b**: IR (film)  $\nu_{\max}$  3078, 2928, 2862, 2840, 1716, 1644, 1459, 1441, 1385, 1364, 1202, 1093, 971  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  5.78 (br t, *J* = 4.5 Hz, 2H), 5.65 (m, 2H), 4.71 (br s, 4H), 4.29 (br s, 4H), 3.18 (m, 8H), 2.61 (dd, *J* = 18.5, 6.7 Hz, 4H), 2.41 (m, 12H), 2.10 (m, 4H), 1.72 (m, 4H), 1.60–1.00 (m, 28H), 0.88 (s, 12H), 0.80 (s, 12H), 0.68 (s, 12H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 100 MHz)  $\delta$  208.6, 207.7, 149.2, 149.1, 126.5, 124.8, 106.4, 55.1, 51.2, 46.4, 41.9, 41.7, 39.1, 38.9, 38.8, 37.4, 33.5, 33.4, 24.4, 22.1, 19.7, 15.0; MS (EI) *m/z* (relative intensity) 502 [ $\text{M}^+$ ] (3), 487 (3), 287 (14), 233 (57), 215 (17), 191 (100), 175 (21), 161 (8), 137 (52). Anal. Calcd for  $\text{C}_{36}\text{H}_{56}\text{O}_2$ : C, 83.02; H, 10.84. Found: C, 82.93; H, 10.81.

(19) Determined by  $^1\text{H}$  NMR.

**9** in very low yields. Therefore, the terminal double bond, required for the metathesis reaction, was built in two steps from the corresponding intermediates **10** and **11**. Thus, amide **2** was reacted with 4-lithiobenzaldehyde dimethyl acetal, yielding **10** in 99% yield. Treatment of **10** with PTSA monohydrate afforded the corresponding aldehyde, which was submitted to Lebel's methylenation conditions ( $[\text{RhCl}(\text{P}(\text{Ph}_3)_3]/\text{Ph}_3\text{P}$ , *i*-PrOH/ $\text{TMSCHN}_2$ ) to yield ketone **8** in 64% overall yield from amide **2** (Scheme 4). A similar procedure

Scheme 4



was used to anchor the ferrocenyl fragment of ketone **9**.<sup>23</sup> This time, the reaction of amide **2** with lithioferrocene-1,3-dioxolane gave ketone **11**.<sup>24</sup> Without further purification, **11** was treated with PTSA affording the corresponding keto aldehyde, which was submitted to methylenation using Lebel's

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(21) The  $\gamma,\delta$ - to  $\alpha,\beta$ -unsaturated ketone isomerization (**3b** to **6**) may be due to the active participation of Grubbs' catalyst in the hydride transfer. However, this process requires the addition of alcohols and bases to the reaction mixture. See: Schmidt, B. *Chem. Commun.* **2004**, 742 and the pertinent references therein. In our case, the increased yield of **6** in toluene pointed to an uncatalyzed thermal isomerization rather to the participation of Grubbs' catalyst.

(22) Fráter, G.; Helmlinger, D.; Kraft, P. *Helv. Chim. Acta* **2003**, 86, 678.

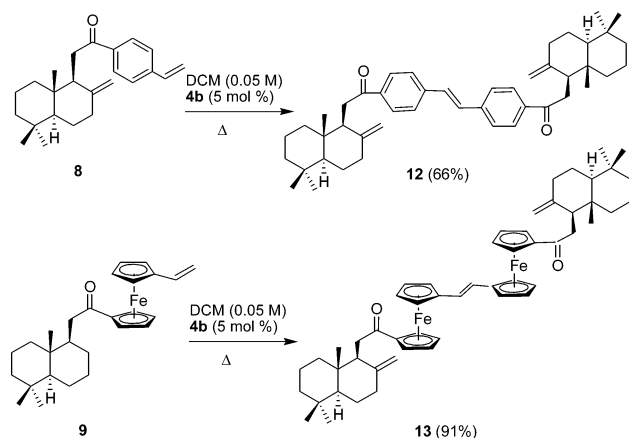
(23) The following procedure was used to prepare compound **9**: To a solution of  $[\text{RhCl}(\text{PPh}_3)_3]$  (95 mg, 0.10 mmol) and  $\text{PPh}_3$  (370 mg, 1.4 mmol) in THF at rt were sequentially added *i*-PrOH (8.8 mL, 1.4 mmol) and 570 mg, (1.3 mmol) of the corresponding aldehyde in 8 mL of THF. The mixture was stirred for 10 min to dissolve the catalyst, treated with  $\text{TMSCHN}_2$  (0.90 mL, 1.8 mmol, 2.0 M solution in  $\text{Et}_2\text{O}$ ), and stirred at rt during 45 min. The reaction mixture was diluted with water and extracted with AcOEt. The combined organic layers were dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to yield 220 mg (39%) of **9** as a red oil:  $[\alpha]_D^{25} = +140.6$  (c 0.34,  $\text{CHCl}_3$ ); IR (film)  $\nu_{\max}$  3085, 2929, 2868, 2844, 1673, 1452, 1380, 1066  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz)  $\delta$  6.34 (dd, *J* = 17.5, 10.7 Hz, 1H), 5.35 (d, *J* = 17.5 Hz, 1H), 5.13 (d, *J* = 10.7 Hz, 1H), 4.75 (br s, 1H), 4.72 (br s, 2H), 4.44 (br s, 1H), 4.41 (br s, 2H), 4.34 (br s, 2H), 4.23 (br s, 2H), 2.83 (dd, *J* = 16.7, 9.4 Hz, 1H), 2.67 (dd, *J* = 16.7, 3.4 Hz, 1H), 2.61 (br d, *J* = 9.4 Hz, 1H), 2.39 (ddd, *J* = 11.4, 3.7, 2.3 Hz, 1H), 2.14 (td, *J* = 12.9, 5.6 Hz, 1H), 1.75 (m, 1H), 1.65–1.10 (m, 7H), 0.90 (s, 3H), 0.83 (s, 3H), 0.76 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz)  $\delta$  199.4, 149.2, 141.7, 136.6, 135.9, 128.3, 126.3, 116.5, 106.4, 55.3, 51.5, 41.9, 39.2, 39.0, 37.5, 34.2, 33.6, 33.5, 23.9, 21.7, 19.3, 14.8; MS (EI) *m/z* (relative intensity) 444 [ $\text{M}^+$ ] (100), 426 (2), 411 (3), 254 (6), 239 (35), 211 (21), 153 (5), 121 (6), 91 (12). Anal. Calcd for  $\text{C}_{28}\text{H}_{36}\text{FeO}$ : C, 75.67; H, 8.16. Found: C, 75.73; H, 8.10.

(24) Regioisomeric derivatives were also detected in the crude reaction mixture.

conditions as described before. Ketone **9** was obtained in 18% overall yield from amide **2**.<sup>25</sup>

The cross-metathesis reactions of alkenes **8** and **9** were performed under the usual conditions giving the corresponding aromatic **12** and bis-ferrocenyl **13** tethered dimers in 66% yield and 91%, respectively, and as single isomers through the newly formed double bond (Scheme 5). In this case, the

Scheme 5



stereochemistry of the double bond was not unambiguously ascertained. Nevertheless, we assume that it should be *E*, as

(25) It should be noted that ferrocenyl derivatives **11** and **9** are labdane organometallic hybrids.

the major reaction product of the cross-metathesis reaction of substrates **3b** and **3c**. Preparation of compounds **12** and **13** demonstrates the suitability of this approach to access  $\alpha$ -onoceradiene analogues having tailored tethers. Further, compound **13** having a ferrocene dimer is a bio-organometallic derivative of this system.

In summary, different  $\alpha$ -onoceradiene-like derivatives have been easily accessed using a cross-metathesis reaction. Structural diversity may be introduced by switching the fragment carrying the double bond during the addition to the starting amide **2**. The use of this approach on the preparation of other homodimers is underway in our laboratories.

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**Supporting Information Available:** Full experimental details for the preparation of the compounds listed in this paper as well as listed spectroscopic and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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