EurJOC European Journal of Organic Chemistry

SHORT COMMUNICATION

DOI: 10.1002/ejoc.201301616

Jatrophane Diterpenes: Preparation of the Western Fragment of Pl-3

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Keywords: Natural products / Total synthesis / Medicinal chemistry / Terpenoids / Oxidation / Lithium

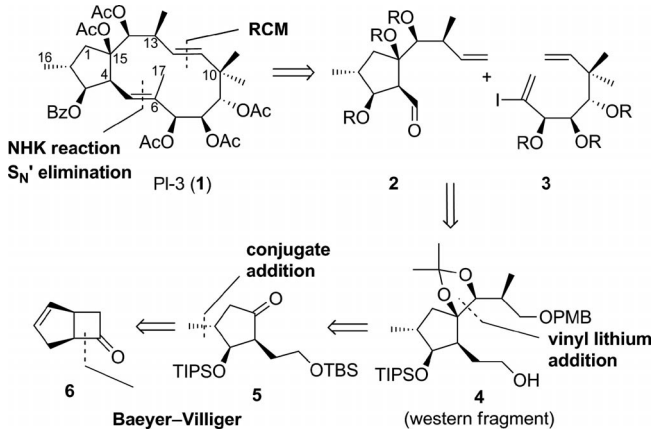
Jatrophane diterpenes are structurally intriguing natural products with promising biological properties. Herein, the synthesis of the western fragment of the Euphorbiaceae constituent Pl-3 starting from (1*R*,5*S*)-bicyclo[3.2.0]hept-2-en-6-one is described. Key steps in the sequence include a Baeyer–Villiger oxidation, an iodolactonization reaction, and the installation of the northern side chain through the addition of a lithiated vinyl bromide. The overall efficiency of the route is increased by taking advantage of latent symmetry.

Introduction

The genus *Euphorbia* belongs to the Euphorbiaceae family and is considered to be one of the largest genera in the plant kingdom, consisting of more than 2000 known species.[1] Members of this plant family, also commonly referred to as spurges, are endemic in tropical and subtropical regions but can also be found in temperate climate zones. The milky latex of *Euphorbia* plants is a rich source of structurally complex and compelling terpene-based natural products. Since the isolation of jatrophone in 1970,[2] more than 300 different compounds have been isolated. The chemical constituents, mostly diterpenes from the tigliane, ingenane, daphnane, and jatrophane families, show a wide range of biological activities. Among those, multidrug resistance modulating properties, as well as antiproliferative activity, particularly found in jatrophane diterpenes, are most important.[3]

Despite the fascinating structural features and diverse biological properties of the large number of Euphorbiaceae constituents isolated so far, only a few have been synthesized up to now.[4] In recent years, various synthetic strategies toward different jatrophane diterpenes have been presented.[5] Prompted by the pharmacological properties of jatrophane diterpenes as well as the challenging structural features of the terpene-based natural products, we concentrate on the synthesis of Pl-3 (**1**). The jatrophane diterpene Pl-3 consists of a highly oxygenated *trans*-fused bicyclo[10.3.0]pentadecane skeleton and was isolated in 2003 by Hohmann and co-workers from *Euphorbia platyphyllos*, a glabrous or pubescent annual plant that occurs mainly in the southern parts of Europe.[6] Recently, we presented a short and general approach toward five-membered ring synthons suitable for the preparation of various jatrophane diterpenes.[5h] Herein, we report a conceptually different and improved route toward the western fragment of Pl-3.

As outlined in the retrosynthetic analysis (Scheme 1), a ring-closing metathesis (RCM) reaction is intended to be the final key step to close the 12-membered macrocycle. The RCM precursor is envisaged to be prepared by a Nozaki–Hiyama–Kishi (NHK) coupling reaction of aldehyde **2** and vinyl iodide **3** with subsequent reductive alkene shift (C6–C17 to C5–C6 double bond, jatrophane numbering).[7] This strategy takes advantage of the comprehensive work performed by Hiersemann and co-workers on their way to (–)-15-*O*-acetyl-3-*O*-propionylcharaciol. The Hiersemann group was able to demonstrate that, although the C12–C13 ring closure can be accomplished by a RCM reaction, this reaction is not feasible for the elaboration of the sterically congested trisubstituted C5–C6 double bond.[4e,5d] The



Scheme 1. Retrosynthetic analysis (TIPS = triisopropylsilyl, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl).

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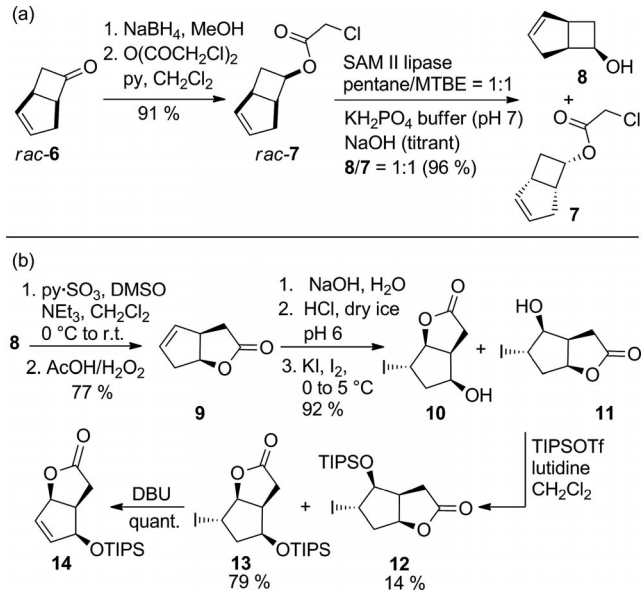
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301616.

elaboration of aldehyde **2** from intermediate **4** requires the removal of carbon C6, which will be accomplished through elimination and subsequent ozonolytic cleavage, as previously demonstrated by the Hiersemann group.[4e] Cyclopentyl fragment **4** should become accessible from bicyclic ketone **6** by Baeyer–Villiger oxidation, an iodolactonization, and a vinyllithium coupling reaction as key steps.

Results and Discussion

The synthesis of **14** commenced with enantiomerically pure bicyclo[3.2.0]hept-2-en-6-ol (**8**), as outlined in Scheme 2. This building block became available on a multigram scale from racemic ketone *rac*-(**6**) through diastereoselective reduction with sodium borohydride, followed by esterification with chloracetic anhydride and subsequent enzymatic resolution of chloroacetate *rac*-**7** (Scheme 2, a).[8] Oxidation of the alcohol functionality in **8** (Scheme 2, b) delivered enantiomerically pure bicyclic ketone **6**, which was converted into lactone **9** by treatment of the alkene with aqueous hydrogen peroxide in acetic acid. Lactone **9** was obtained as the sole product of the Baeyer–Villiger oxidation in excellent yield.[9]

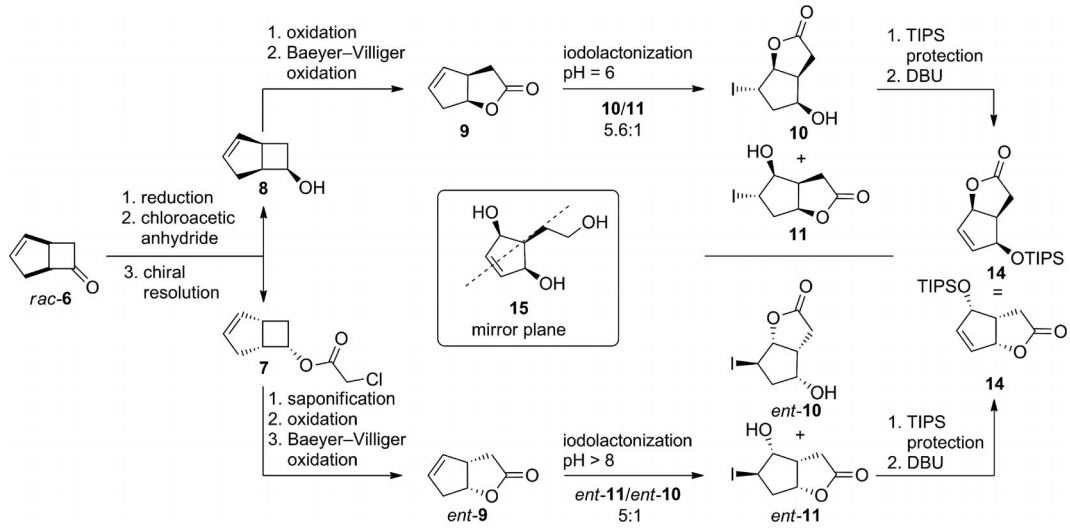


Scheme 2. Preparation of lactone **14** (py = pyridine, MTBE = methyl *tert*-butyl ether, Tf = trifluoromethanesulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene).

Next, we turned our attention to the functionalization of the double bond. As iodolactonization was identified as the most feasible procedure to elaborate the stereochemical pattern present in the natural product, lactone **9** was allowed to react with iodine under different reaction conditions. The iodolactonization showed a distinct pH-dependent product formation. Whereas desired iodolactone **10** was favored at pH 6, **11** was isolated as major product if the pH was higher than 8. The inseparable mixture of iodolactones could be easily separated by flash column chromatography after formation of corresponding silyl ethers **12** and **13**.[10]

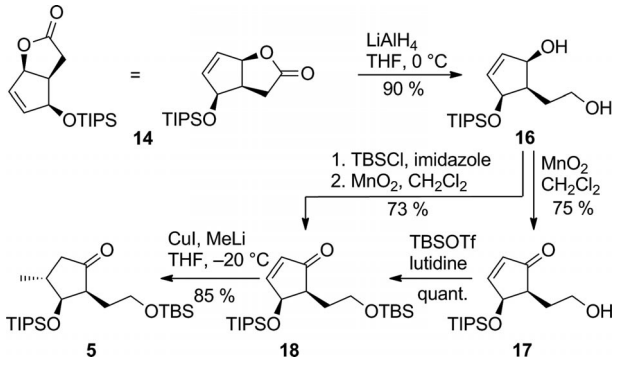
As the originally envisioned direct methylation of the iodide could not be achieved, we decided to follow a slightly modified approach and targeted the installation of the methyl functionality by conjugate addition. Thus, cyclopentene **14** was prepared in quantitative yield through DBU-mediated elimination of the iodide in **13**. At that point, the great advantage of the latent symmetry in cyclopentene **14** became evident, as the mirror plane present in the substrate (shown in unprotected intermediate **15**, Scheme 3) allowed the conversion of antipodal alcohol *ent*-**8** into enantiomerically pure lactone **14** (Scheme 3). The "enantiomeric switch" was accomplished simply by adjusting the pH during the iodolactonization reaction. As a consequence of the symmetry, both enantiomers of alcohol **8** were efficiently converted into lactone **14**.

Reduction of the lactone functionality in **14** with lithium aluminum hydride afforded diol **16** in excellent yield (Scheme 4). Next, silylation of the primary hydroxy functionality, followed by allylic oxidation delivered enone **18**,



Scheme 3. Advantage of latent symmetry in the synthesis of **14**.

which served as the substrate for the conjugate addition reaction. Although enone **18** was also accessible in comparable yield by performing the reaction sequence in reverse order, that is, allylic oxidation followed by silylation with TBS-triflate (via **17**), the initial route was favored because of the lower cost of the reagents. Selective 1,4-addition of a methyl cuprate afforded five-membered ring synthon **5** in excellent yield as a single isomer. The preparation of **5** is easily scalable and the short reaction sequence allowed perfect control of all stereogenic centers.

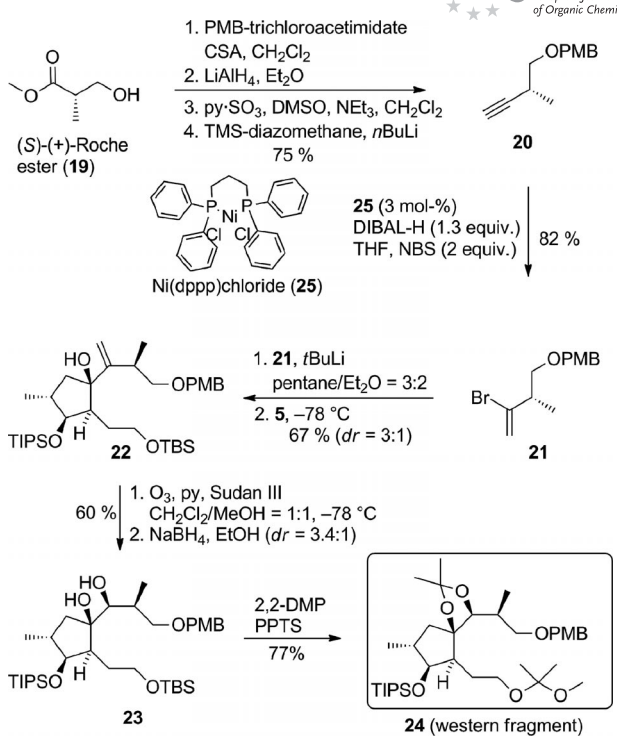


Scheme 4. Preparation of ketone **5**.

Vinyl bromide **21** was prepared in five steps from commercially available (*S*)-(+)-Roche ester (**19**), as shown in Scheme 5. Protection of the hydroxy functionality as a PMB ether was followed by a reduction/oxidation sequence to access the corresponding aldehyde. Next, C1 elongation with TMS-diazomethane afforded alkyne **20** in good overall yield. Vinyl bromide **21** was isolated after regioselective hydroalumination catalyzed by nickel catalyst **25** and subsequent addition of *N*-bromosuccinimide (NBS), following Hoveyda's protocol.[11]

Alkylation of ketone **5** with lithiated vinyl bromide **21** proved to be a tedious task. Whereas the addition of vinylmagnesium bromide as test substrate afforded the corresponding tertiary alcohol in nearly quantitative yield, desired product **22** was not obtained by employing the Grignard reagent derived from vinyl bromide **21**. Reaction of **21** with sodium naphthalide and coupling under Barbier-type conditions also did not solve the problem. Next, bromide **21** was converted into the corresponding boronate and employed in transition-metal-catalyzed coupling reactions, also without success. Finally, the problem was solved upon lithiation of bromide **21** with *t*BuLi in a solvent mixture of pentane/diethyl ether in a ratio of 3:2, followed by slow addition of ketone **5** to the lithiated species. Desired adduct **22** was obtained in 67% yield as a 3:1 diastereomeric mixture, favoring the desired isomer. A detailed discussion of all coupling attempts is provided in the Supporting Information.

Next, ozonolytic cleavage of the exomethylene functionality in the presence of Sudan III as indicator to prevent benzylic oxidation of the PMB protecting group was followed by selective reduction with sodium borohydride in ethanol, and advanced diol **23** was isolated in a 3.4:1 dia-



Scheme 5. Synthesis of the western fragment of Pl-3 (CSA = camphorsulfonic acid, DIBAL-H = diisobutylaluminum hydride, 2,2-DMP = 2,2-dimethoxypropane, PPTS = pyridinium *para*-toluenesulfonate).

stereomeric ratio. The synthesis of the western fragment of Pl-3 was concluded after protection of **23** as an acetonide with concomitant cleavage of the primary silyl ether and protection of the resulting primary alcohol as a ketal. Finally, intermediates **24** and **26** (prepared through acetonide protection of the undesired diastereomeric diol, which was afforded after reduction of ozonolysis product of **22**; see the Supporting Information) served to unambiguously define the relative relationship of all stereogenic centers through NOE correlation studies, as outlined in Figure 1.

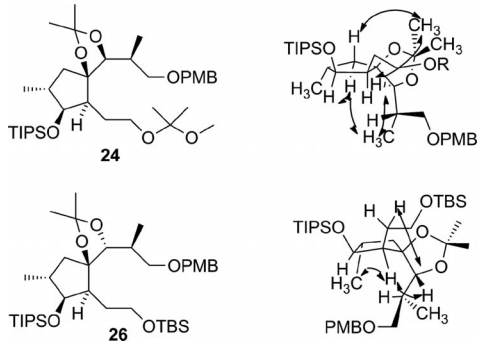


Figure 1. NOE correlations in cyclopentanes **24** and **26**.

Conclusions

Summarizing, the synthesis of the western fragment of Pl-3 was achieved in a short and stereoselective manner.

Importantly, the overall efficiency of the route was greatly improved by taking advantage of the latent symmetry present in lactone **14**, which allowed the use of both enantiomeric forms of bicyclic alcohol **8** as a starting material for the preparation of **24**. The utilization of **24** in the preparation of Pl-3 is currently under investigation, and further results will be reported in due course.

Experimental Section

(3a*R*,6a*S*)-3,3a,6,6a-Tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (9):[9,12] To a solution of **6** (9.76 mL, 92 mmol, 1.0 equiv.) in acetic acid (237 mL) and water (26 mL) was added a solution of H_2O_2 (30% in water, 22.7 mL, 222 mmol, 2.4 equiv.) in acetic acid (195 mL) and water (22 mL) at 0 °C. The mixture was stirred for 24 h at 0 °C before water (200 mL) was added. The crude product was extracted with CH_2Cl_2 (6× 200 mL), and the combined organic extract was washed with aqueous Na_2SO_3 (10%, 200 mL) and saturated $NaHCO_3$ (600 mL). ***Note:*** Vigorous formation of CO_2 was observed. The workup must be performed with great care! The organic layer was dried with $MgSO_4$ and reduced in vacuo. The product was purified by kugelrohr (bulb-to-bulb) distillation to afford **9** (10.2 g, 88%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.80–5.78 (m, 1 H), 5.59–5.57 (m, 1 H), 5.15–5.11 (m, 1 H), 3.53–3.49 (m, 1 H), 2.80–2.71 (m, 3 H), 2.47–2.42 (m, 1 H) ppm. $[\alpha]_D^{20}$ = –102.3 (*c* = 1.03, $CHCl_3$), m.p. 42–43 °C.

(3a*S*,4*S*,6*S*,6a*S*)-4-Hydroxy-6-iodohexahydro-2*H*-cyclopenta[*b*]-furan-2-one (10):[10] Lactone **9** (1.0 g, 8.06 mmol, 1.0 equiv.) was added to a solution of NaOH (0.80 g, 20 mmol, 2.48 equiv.) in water (41 mL). After stirring for 30 min at room temperature, the resulting homogeneous solution was cooled to 0 °C and HCl (32 wt.-% in water, 1.9 mL, 19.7 mmol, 2.44 equiv.) was added. After stirring for approximately 30 s, pH 6 was obtained by the addition of dry ice. A solution of KI (12.04 g, 72.5 mmol, 9.0 equiv.) and I_2 (6.13 g, 24.17 mmol, 3.0 equiv.) in water (21 mL) was added in one portion. The mixture was allowed to stir for 24 h between 0 and 5 °C before the reaction mixture was diluted with CH_2Cl_2 (150 mL) and quenched by the addition of solid Na_2SO_3 (addition until a clear yellow solution over a white precipitate was observed). The resulting colorless solution was saturated with Rochelle's salt and extracted exhaustively with CH_2Cl_2. To quantitatively transfer the reaction product into the organic phase, the mixture was extracted at least 10 times (80 mL CH_2Cl_2 each time, progress was monitored by TLC analysis). The combined organic layer was washed with brine (200 mL), dried with $MgSO_4$, and concentrated in vacuo. Purification of the crude product by flash column chromatography (pure toluene to toluene/EtOAc, 5:1) afforded an inseparable mixture of **10** and **11** (2.0 g, 92%) as a slightly yellow oil. The mixture was used for the next step without further purification.

(1*R*,2*S*,3*S*,4*R*)-2-{2-[(*tert*-Butyldimethylsilyl)oxy]ethyl}-1-{(*R*)-4-[(4-methoxybenzyl)oxy]-3-methylbut-1-en-2-yl}-4-methyl-3-[(triisopropylsilyl)oxy]cyclopentan-1-ol (22): To a solution of bromide **21** (0.255 g, 0.896 mmol, 1.2 equiv.) in Et_2O/pentane (3:2, 4.0 mL) was added a solution of *tert*-butyllithium (1.7 M in pentane, 0.92 mL, 1.57 mmol, 2.1 equiv.) at –78 °C. After 30 min at that temperature, the reaction mixture was allowed to stir at room temperature for 5 min. After recooling of the slightly yellow mixture to –78 °C, a solution of **5** (0.320 g, 0.746 mmol, 1.0 equiv.) in Et_2O/pentane (3:2; 3.5 mL) was added slowly (over a period of 10 min). Stirring at that temperature was continued for 5 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (20 mL). The layers were separated, and the aqueous phase was extracted with EtOAc (3× 20 mL). The combined organic layer was washed with brine (50 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc, 40:1) to afford **22** (0.237 g, 50%) as a colorless oil with the corresponding C1 epimer (**S10**, see Supporting Information) as a side product (80 mg, 17%). ***Note:*** The exact ratio of the solvents is essential for the success of this reaction. Et_2O and pentane, freshly distilled from sodium, were mixed in a 3:2 ratio, and this solvent mixture was stored over molecular sieves (3 Å) prior to use. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.24 (m, 2 H), 6.89–6.85 (m, 2 H), 5.28 (s, 1 H), 4.91 (s, 1 H), 4.48 (d, *J* = 11.6 Hz, 1 H), 4.38 (d, *J* = 11.6 Hz, 1 H), 4.11 (d, *J* = 3.8 Hz, 1 H), 4.00 (s, 1 H), 3.80 (s, 3 H), 3.69 (ddd, *J* = 9.8, 6.9, 4.7 Hz, 1 H), 3.63–3.57 (m, 1 H), 3.46 (dd, *J* = 9.1, 4.9 Hz, 1 H), 3.28 (dd, *J* = 9.1, 9.1 Hz, 1 H), 2.44–2.23 (m, 2 H), 2.08 (ddd, *J* = 10.0, 3.3, 3.3 Hz, 1 H), 1.85 (dddd, *J* = 14.4, 9.8, 5.0, 4.9 Hz, 1 H), 1.63–1.57 (m, 1 H), 1.61 (dd, *J* = 13.9, 3.3 Hz, 1 H), 1.15 (d, *J* = 6.8 Hz, 3 H), 1.13–1.09 (m, 21 H), 0.98 (d, *J* = 7.1 Hz, 3 H), 0.88 (s, 9 H), 0.03 (s, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.24 (C), 153.93 (C), 131.05 (C), 129.25 (CH), 113.85 (CH), 109.31 (CH_2), 86.17 (C), 83.27 (CH), 75.91 (CH_2), 72.72 (CH_2), 62.15 (CH_2), 55.41 (CH_3), 47.86 (CH_2), 45.35 (CH), 40.17 (CH), 34.81 (CH), 26.12 (CH_3), 25.41 (C), 20.80 (CH), 20.42 (CH), 18.30 (CH_3), 12.72 (CH), –5.16 (CH_3) ppm. HRMS (ESI): calcd. for $C_{36}H_{66}NaO_5Si_2$ $[M + Na]^+$ 657.4346; found 657.4332 ± 5 ppm. $[\alpha]_D^{20}$ = +3.7 (*c* = 0.81, $CHCl_3$). IR (ATR): $\tilde{\nu}$ = 3494, 2954, 2866, 2360, 2341, 1716, 1613, 1586, 1540, 1513, 1462, 1386, 1360, 1248, 1220, 1097, 1031, 882, 834, 774, 669, 657 cm^{-1}.

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ^{1}H NMR and ^{13}C NMR spectra of all compounds.

Acknowledgments

R. F. is a recipient of a DOC-fFORTE-fellowship of the Austrian Academy of Sciences at the Department of Organic Chemistry, University of Vienna. The Austrian Science Fund (FWF) (Fonds zur Förderung der wissenschaftlichen Forschung) is gratefully acknowledged for financial support (Project FWF-P20697-N19). The authors thank Dr. Hanspeter Kählig (University of Vienna) for assistance with NMR spectroscopy.

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Received: October 28, 2013
Published Online: January 8, 2014

