Synthesis of-3-(*tert*-butyldimethylsilyoxy)-4-Isopropylcyclopentanone (4)

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Abstract

In this research the preparation of target compound was completed in three sequential steps. Starting from furfural alcohol (1) that was converted to racemic 4-hydroxycyclopent-2-enone (2) in 39% yield after treated with catalytic amount of KH_2PO_4 in water as a solvent. Protection of the free hydroxyl group in **(2)** with *t*-butyldimethylsilyl chloride in the presence of DMAP was the next step to furnish compound **(3)** in yield of 50%. Organocuprate conjugate addition on (3) provide compound (4) in yield of 50%.

Key words: furfural alcohol, isopropyl group, dimethyl amine pyridine, conjugated addition

تحضير وتشخيص المركب
3-(*tert*-butyldimethylsilyoxy)-4-isopropylcyclopentanone (4)

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الخلاصة

تم في هذا البحث تحضير وتشخيص المركب المطلوب **3-(*tert*-butyldimethylsilyoxy)-4-isopropylcyclopentanone (4)** بثلاث خطوات متتابعة. تضمنت الخطوة الاولى تحضير الكيتون **4-hydroxycyclopent-2-enone (2)** على هيئة مزيج راسيمي بنسبة ناتج 39% من تفاعل فورفورال الكحول (1) مع فوسفات البوتاسيوم ثنائي الهايدروجين (KH_2PO_4) بوجود الماء كمذيب. تحول مجموعة الهيدروكسيل الحرة للمركب المذكور اعلاه (**2**) إلى TBDMS بوجود ثلاثي المثيل سايلل كلورايد (TSM-Cl) والعامل المساعد 4,4 ثنائي مثل امين بردين(DMAP) كانت الخطوة الثانية في هذا العمل لتعطي المركب **4-*tert*-butyldimethylsilyloxy-2-cyclopentenone (3)** بنسبة ناتج 40%. الكلة المركب الكيتوني غير المشبع رقم (**3**) مع كاشف organo-cuprate عن طريق الاضافة من نوع (1,4) اعطى المركب المطلوب (4) بنسبة ناتج 50%

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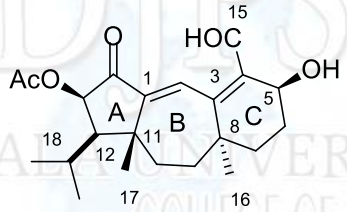
Introduction

For thousands of years, natural products have played an important role throughout the world in treating and preventing human diseases.[1]In recent years a number of modern drugs have been derived from natural sources, and it has been estimated that over 40% of medicines are derived from natural sources. [2] Antibiotic resistance in bacteria has become a serious problem worldwide. Guanacastepene A has shown significant antibiotic activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin resistant *Enterococcus faecalis* (VREF).[3,4] However, guanacastepene A like other antibiotics has side-effects; it induces haemolytic activity against human red blood cells (RBC).[5] Due to its novel carbon skeleton (5-7-6) fused tricyclic system and the possibility of exploring activity guanacastapene family in other biological systeme, It is not surprising that the total synthesis of the skeleton of guanacastepene A has received much attention from synthetic chemists in the past few years



Guanacastepene A

Guanacastepene A was the first member of a unique family of diterpene natural products to be discoverd in **2000**, by Clardy*et al* from an unclassified endophytic fungus, found growing on a branch of *Daphnopsisamericana*, a tree indigenous to Costa Rica's Guanacaste conservation area.[6]The initial approach to the synthesis of natural product 6 and 7 ring system focused on the preparation of the desired A-ring precursor on a suitable scale that would enable the synthesis of the required target guanacastepene A.

Experimental

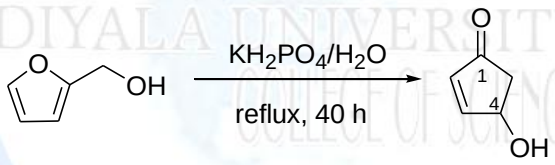
Experimental Techniques

^{1}H NMR spectra were recorded on either a Bruker –Avance III 400 (400 MHz) or a Bruker DPX250 (250 MHz) spectrometer. Signal positions are recorded as chemical million (ppm). ^{13}C NMR spectra were recorded on the same spectrometers at either 62.5 or 100 MHz.Infrared

spectra were record on a Perkin Elmer 1720X spectrometer. Spectra were recorded as thin liquid films between sodium chloride plates. Mass spectra (*m/z*) and accurate mass measurements (HRMS) were recorded under conditions of chemical ionisation (CI) using ammonia as the ionising source. The instrument used was a Thermo Scientific LTQ Orbitrap XL Accela LC. Thin layer chromatography (TLC) analyses were performed using plastic backed plates with 0.25 mm Merck 60 G silica gel with fluorescent indicator. TLC plates were developed either by the quenching of UV fluorescence at 254 nm or by treatment with a basic $KMnO_4$ solution or vanillin, and heating.Reactions that required anhydrous conditions were carried out under nitrogen in flame-dried glassware equipped with aseptum-capped inlet connected to a nitrogen cylinder.Reagents were obtained from Sigma Aldrich and used without further purification.

Experimental Procedures

Synthesis of 4-hydroxycyclopent-2-enone (2)[7]



(1) **(2)**

A solution of furfuryl alcohol (11.04 mL, 127. 39 mmol) in water (370 mL) was treated with KH_2PO_4 (0.63 g, 4.62 mmol), and heated to reflux for 40 h. The solution was cooled to rt., and extracted with CH_2CI_2(200 mL). The organic layer was washed with water (500 mL) and the solvent removed *invacuo* to give a red oil. The red oil was then redissolved in CH_2CI_2 (50 mL) and dried over $MgSO_4$. Filtration and evaporation of the solvent *invacuo*

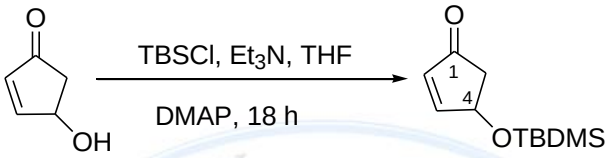
gave **(2)** as a dark red oil (.3 g, 39%)

IR (thin film) $\nu_{(max)}$ cm^{-1}: 3411 (O–H), 2918, 2352, 1712 (C=O), 1698, 1339, 1186, 1103, 1046, 942, 796; δ_H (400.1 MHz, $CDCl_3$): 7.57 (1H, dd, *J* 5.7 and 2.4 Hz, H-3), 6.25 (1H, dd, *J* 5.7 and 1.3 Hz, H-2), 5.04–5.08 (1H, m, H-4), 2.83 (1H, dd, *J* 18.5 and 6.0 Hz, H-5) 2.31 (1H, dd, *J* 18.5 and 2.0 Hz, H-5); δ_C(100.6 MHz, $CDCl_3$): 207.6 (C-1), 163.4 (C-3), 135.1 (C-2),

70.4 (C-4), 44.7 (C-5); HRMS (CI) *m/z*: 99.0441 $[M + H]^+$;Calculated for$[C_5H_6O_2+H]^+$ 99.0368.

Synthesis of 4-*tert*-butyldimethylsilyloxy-2-cyclopentenone(3)[7]

Method A:



(2) **(3)**

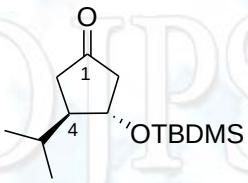
A solution of 4-hydroxycyclopent-2-enone **(2)** (6.4 g, 65.2 mmol) and Et_3N (14.0 mL, 100.4 mmol) in anhydrous THF (33 mL) was treated with DMAP (0.16 g, 1.3 mmol). The solution was cooled to 0 ^oC, *t*-butyldimethylsilylchloride (9.3 g, 61.7 mmol) was added portionwise over 10 minutes at or below 10 ^oC and the resulting mixture was stirred at room temperature for 18 h and then quenched by the addition of aqueous HCl (0.5 M, 250 mL). The phases were separated and the aqueous layer was extracted with hexane (3 × 50 mL). The organic layers were combined and washed sequentially with aqueous HCl (2 × 50 mL, 0.5 M HCl), $NaHCO_3$ (50 mL, 5% $NaHCO_3$) and a saturated aqueous solution ofNaCl (50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo* affording crude 4-*tert*-butyldimethylsilyoxy-2-cyclopentenone**(3)**. Distillation with a Kugelrohr[8] apparatus under reduced pressure furnished the title compound (**383**) as pale yellow oil (5.5 g, 40 %); IR (thin film) $\nu_{(max)}$ cm^{-1}: 2954, 2929, 2856, 1723 (C=O), 1471, 1404, 1354, 1252, 1182, 1108, 1071, 1005, 956, 900, 836, 777, 669; δ_H (400.1 MHz, $CDCl_3$):7.36 (1H, dd, *J* 5.6

and 2.0 Hz, H-3), 6.09 (1H, dd, *J* 5.7 and 1.3 Hz, H-2), 4.87–4.90 (1H, m, H-4), 2.63 (1H, dd, *J* 18.0 and 6.0 Hz, H-5), 2.17 (1H, dd, *J* 18.0 and 2.0 Hz, H-5), 0.80 (9H, s, 4-Si$(CH_3)_2$C$(CH_3)_3$), 0.02 (3H, s, 4-Si$(CH_3)_2$C$(CH_3)_3$), 0.01 (3H, s, 4-Si$(CH_3)_2$C-$(CH_3)_3$); δ_C (100.6 MHz, $CDCl_3$): 206.4 (C-1), 163.8 (C-3), 134.4 (C-2), 70.8 (C-4), 44.9 (C-5), 25.7 (4-Si$(CH_3)_2$C$(CH_3)_3$), 18.0 (4-Si$(CH_3)_2$C$(CH_3)_3$), -4.7 (4-Si$(CH_3)_2$C$(CH_3)_3$); HRMS (CI) *m/z*: 213.1312 $[M + H]^+$; Calculatedfor $[C_{11}H_{20}O_2Si + H]^+$ 213.1233.

Method B:[9]

To solution of 4-hydroxycyclopent-2-enone **(2)** (3 g, 30.6 mmol) in anhydrous CH_2Cl_2 (60 mL) at 0 ^oC was added imidazole (2.7 g, 39.6 mmol), followed by *tert*-butyldimethylsilychloride (4.6 g, 30.5 mmol) and a catalytic amount of dimethylaminopyridine (10 mg, 0.08 mmol). The mixture was allowed to warm slowly to room temperature for 18 h. The orange mixture was quenched with a saturated aqueous solution of Na_2HCO_3 (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL), dried over $MgSO_4$ and evaporated to yield a red oil. Purification of the product by distillation under reduced pressure using a 10 cm tall Vigreux column afforded the desired compound **(3)** as a yellow oil (2.7 g, 42%) b.p. 100–110 ^oC/3mbar.

Synthesis of-3-(*tert*-butyldimethylsilyoxy)-4-isopropylcyclopentanone (4)[10]



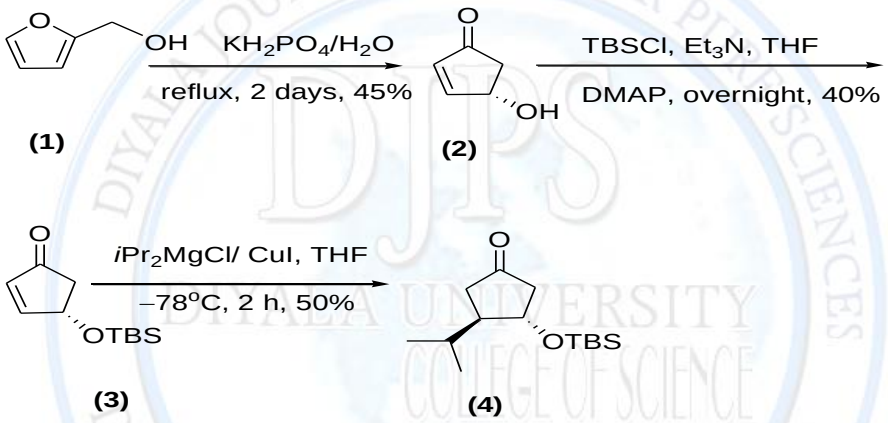
(4)

Isopropyl magnesium chloride(4.7 mL, 2 M solution in THF, 9.4 mmol) was slowly added to a suspension of pre-dried CuI (0.9 g, 4.72 mmol) in anhydrous THF (15 mL), at –78 ^oC under a nitrogen atmosphere. The reaction was stirred for five minutes at room temperature, and then the mixture was re-cooled to –78 ^oC before a solution of 4-*tert*-butyldimethyisilyloxy-2-cyclopentenone **(3)** (0.5 g, 2.35 mmol) in anhydrous THF (5 mL) was added. The reaction was stirred for 2 h at –78 ^oC and then quenched with saturated ammonium chloride (10 mL). The aqueous layer was extracted with ether (3 × 30 mL) and the combined organic extracts were washed with brine and dried over $MgSO_4$. The solvent was removed *invacuo*and the residue was purified by column chromatography on silica, eluting with petroleum ether/ether (9:1) to furnish the title compound as a yellow oil (0.29 g, 50%). IR (thin film) $\nu_{(max)}$ cm^{-1}: 2956, 2845, 1749 (C=O), 1468, 1256, 1112, 1057, 864, 836,775; δ_H(400.1 MHz,$CDCl_3$): 4.15 (1H, q., *J* 7.0 Hz, H-3), 2.46 (1H, dd, *J* 12.0 and 1.5 Hz, H-2), 2.34 (1H, ddd, *J* 12.0, 9.0, and 1.5 Hz, H-5), 2.13 (1H, ddd, *J*12.0, 5.5, and 1.5 Hz, H-2), 1.91–1.95 (1H, m, H-4), 1.89 (1H, dd, *J*14.0 and 9.0 Hz, H-5), 1.71 (1H, septet, *J*6.5 Hz, 4-C*H*$(CH_3)_2$), 0.91 (3H, d, *J* 6.5 Hz, 4-CH(C*H*$_3)_2$), 0.83 (3H, d, *J* 6.5 Hz, 4-CH(C*H*$_3)_2$), 0.80 (9H, s, 3-Si$(CH_3)_2$C(C*H*$_3)_3$), −0.01 (3H, s, 3-

$Si(CH_3)_2C(CH_3)_3$, −0.03 (3H, s, $Si(CH_3)_2C(CH_3)_3$); δ_C (100.6 MHz, $CDCl_3$): 216.2 (C-1), 72.1 (C-3), 51.7 (C-4), 48.1 (C-2), 39.3 (C-5), 28.2 (4-*C*H$(CH_3)_2$, 25.7 (3-$Si(CH_3)_2C(CH_3)_3$), 21.5 (4-CH(*C*$H_3)_2$), 18.7 (4-CH(*C*$H_3)_2$), 17.9 (3-$Si(CH_3)_2$*C*$(CH_3)_3$), −4.4 (3-Si(*C*$H_3)_2$C $(CH_3)_3$), −4.8 (3-Si(*C*$H_3)_2$); HRMS (CI) *m/z*: 279.1750 $[M + Na]^+$; Calculated for $[C_{14}H_{28}O_2Si + Na]^+$ 279.1859.

Results and Discussion

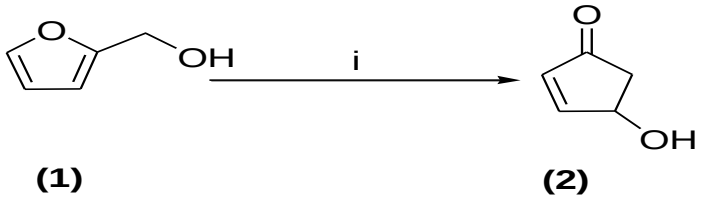
The diastereo controlled conjugate addition to the α,ß-unsaturated ketone **(3)** was the next step towards the construction of the correctly configured A-ring of guanacastepene.



Scheme 1.Proposed synthesis of (4)

Synthesis of 4-hydroxycyclopent-2-enone (2)[7]

The first step in the synthesis of racemic 4-hydroxycyclopent-2 from inexpensive furfuryl alcohol **(1)** that was converted into **(2)** in 39% yield by the procedure of Curran*et al*.[7] A solution of furfuryl alcohol in H_2O was treated with a catalytic amount of KH_2PO_4 and heated to reflux for 40 hours. It was found unnecessary to adjust the pH to 4.1 in the present of H_3PO_4 as the pH was already 4.1 (pH meter), **(Scheme 2)**. In the ^1H NMR spectrum of **(2)** it was possible to observe the presence of a doublet of doublets at δ 7.57 and δ 6.25 ppm, having coupling constants (*J* 5.7, 2.4 Hz) and (*J* 5.7, 1.3 Hz), respectively corresponding to the olefin protons of the double bond of the enone. The IR spectrum also supported the structure, as evidenced by an O–H stretch as a broad band at 3411 cm^{-1} and a strong absorption corresponding to the carbonyl group at 1712 cm^{-1}.



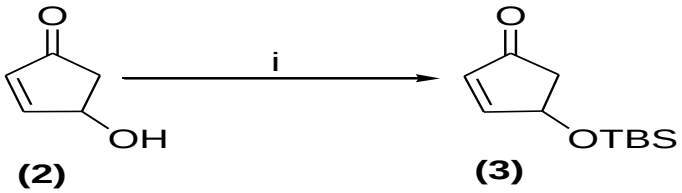
(i) KH_2PO_4, H_2O, reflux, 40 h, 45%

Scheme 2. Preparation of a racemic mixture of **(2)**.

It was found that, when the reaction was conducted on a larger scale (740 mL water, 22 mL furfuryl alcohol, and 1.26 g of KH_2PO_4, reflux, 40 hours), the reaction afforded only a 49% yield of **(2).**

Synthesis of 4-*t*-butyldimethylsilyloxy-2-cyclopentenone (3)

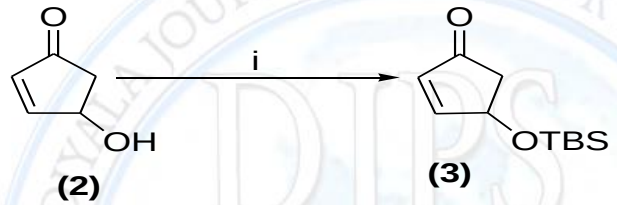
Protection of the free hydroxyl group in **(2)** with *t*-butyldimethylsilyl chloride was achieved following the literature procedure of Curran*et al.*[7]Treatment of 6.4 g of **(2)** with catalytic quantities of DMAP, excess Et_3N and one equivalent of TBDMSCl in anhydrous THF initially at 10^{o}Cfor 10 min and allowing the resulting mixture to stand for 18 hours at room temperature furnished **(3)**. Aqueous work up and purification by short path distillation[8] (b.p. 80-90 ^{o}C/3millbar) afforded **(3)** in a yield of 40% **(Scheme 3)**. The structure was confirmed by analysis of the ^{1}H NMR and IR spectra. A new feature in the ^{1}H NMR spectrum was a singlet at δ 0.80 ppm corresponding to the protons of the *t*-butyl group and signals at δ 0.02 and δ 0.01 ppm corresponding to the protons of the two methyl groups attached to the silicon atom. The disappearance of the hydroxyl absorption in the IR spectrum also confirmed the success of the reaction.



(i) Et_3N, DMAP, TBDMSCl, THF, rt, 18 h, 40%

Scheme 3.Intoduction of the *t*-butyldimethylsilyl protecting group onto (2).

An alternative approach was also investigated using 1.3 equivalents of imidazole, 1 equivalent of TBDMSCl and a catalytic amount of dimethylaminopyridine in anhydrous dichloromethane at 0 ^{o}C to room temperature for 18 hours.[9] The ^{1}H NMR spectrum of the crude product showed that starting material had been consumed with formation the protected silyl compound **(3)**. Purification of the residue was performed by distillation (b.p. 100-110 ^{o}C/3 millbar) using a Vigreux column to furnish the product **(3)** in a yield of 42% as a colourless oil **(Scheme 4)**. It was found that the clear oil started to turn a light red colour on storing at room temperature. However, the ^{1}H NMR spectrum of this sample did not show any decomposition and the peaks of the product **(383)** were in agreement with the data published in the literature.



(i) Imidizol, TBDMSCl, DMAP, 0^{o}C to rt, CH_2Cl_2, 18 h, 42%

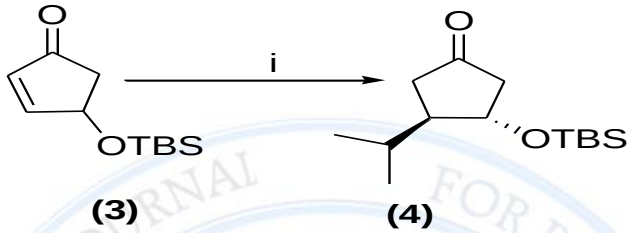
Scheme 4.Alteranative method to introduce *t*-butyldimethylsilyl group onto (2).

Synthesis of 4-(*tert*-butyldimethylsilyoxy)-3-isopropylcyclopentanone (4)

the first attempt at conjugate addition, the procedure of Yakura*et al*.[10] was followed using isopropylmagnesium chloride. TLC analysis showed that a new more polar spot was formed after two hours, with complete consumption of the starting material. The ^{1}H NMR spectrum of the crude product obtained after work-up indicated a mixture of two disteroisomeric products had formed with gross structures corresponding to the desired target **(4)**.

On purification by column chromatography on silica the major product eluted first and the ^{1}H NMR spectrum of this material indicated two three-proton doublets at δ 0.91 and δ 0.83 ppm (*J* 6.5 Hz) corresponding to the diastereotopic methyl groups of the isopropyl group. Both vinylic protons of the conjugated double bond of the starting material had disappeared, confirming the formation of the desired product **(4)**. In addition, in the ^{13}C NMR spectrum,

two carbon signals at δ 21.5 and δ 18.7 ppm were observed, also corresponding to the diastereotopic methyl groups of the isopropyl group. Loss of the absorption due to the α,β-unsaturated double bond in the IR spectrum and the appearance of a strong absorption at 1749 cm^{-1}corresponding to a saturated carbonyl group in a five membered ring also provided further structural evidence for the formation of **(4) (Scheme 5)**.



(3) **(4)**

(i) *i*PrMgCl, CuI,THF,–78°C, 2 h, 50%

Scheme 5.Organocuprateconjugate addition on (3).

The next product to elute from the column was found to be the miner diastereoisomer that could not be separated from the major distereoisomer by column chromatography; consequently a mixture of the two distereoisomers was obtained after column chromatography. The presence in the ^{1}H NMR spectrum of two doublets at δ 0.97 and 0.93 ppm (*J* 6.4 Hz) was indicative of the second stereoisomer. On the basis of this result, the mixture of minor and major isomers was obtained in a ratio of 1:3.

Finally a small quantity of starting material **(3)** (9 mg) was isolated from the latter fraction, in spite of it appearing to have been totally consumed according to TLC analysis.The moderate yield in this reaction is possibly due to the steric constraints imposed by the bulky protecting group, hindering approach of the organometallic reagent. The results are summarized in **Table (1)** to allow the comparison of the data obtained, for each case.

Table 1.Study of the formation of (44) under different conditions

ENTRY	*I*PRMGCL	CUI	QUANT.	TIME	YIELD	RATIO*
1	4 equiv. 4 equiv.	2 equiv. 2 equiv.	0.5 g 0.3 g	2 h 2h	50% 44%	3:1 †
2	4 equiv.	2 equiv.	1.5 g 2 g	2 h 2 h	33% 33%	3:1 2:1
3	6 equiv.	3 equiv.	0.5 g	2 h	56%	1:1
4	6 equiv.	3 equiv.	1 g 1.5 g 2 g 1.5	2 h 3,30 min 2 h 2 h	46% 44% 43% 39%	† † 2:1 2:1
5	4 equiv.	3 equiv.	1.5 g	2 h	33%	1:1
6	6 equiv.	2 equiv.	0.5 g 2 g	2 h 2 h	55% 45%	† †
7	8equiv.	4 equiv.	0.5 g	2 h	37- 41%	2:1
8	4 equiv.	2 equiv.	1 g	overnight	trace	†
9	4 equiv.	2 equiv	1 g	4 h	50%	†
10	4 equiv. 4 equiv.	2 equiv 2 equiv	1 g 1 g	2 h 2 h	50% 58%	15:1 †

***Ratioof the mixture corresponding to the desired isomer (4) against second isomer**

† Only desired isomer observed in crude mixture

During our investigations to improve the yield of **(4)**, attempts were made to use the previous methodology of Yakura*et al.*[10]The cyclopentenone**(383)** was converted to 4-isopropylcyclopentanone **(384)**by treatmentwith various ratios of isopropylmagnesium chloride to CuI, and the reacton was carried out on different scales of starting material **(383)** with reaction times ranging from two hours to overnight. The yields obtained in all cases were approximately in the same range, butallowing the reaction to warm to room temperature overnight after stirring for 4 hours at –78 ºC afforded only traces of **(384)**. In addition, it was

found in some cases that the second isomer had disappeared; however the yield of the desired compound **(384)** was still obtained between 44-50%.

Confirmation for the *trans* stereochemistry of the major 1,4-adduct **(384)** was achieved by analysis of n.O.e. difference experiments **(Figure 14**).

The n.O.e. experiments and ^{1}H NMR spectrum of **(384)** are shown in **(Figure 15)**. Irradiation of one doublet for the methyl group at C-7 enhanced the signal for proton H-4 by (0.17%) as well as the second methyl group by (0.24%) and the H-7 proton by (0.21%). Irradiating the second methyl group also enhanced the signal from the H-4 proton by (0.44%), the other methyl group by (0.77%) as well as the H-7 proton by (0.82%). Irradiation of proton H-4 enhanced the two methyl groups by (0.88%) and (1.36%) respectively, the H-7 proton by (0.62%) and H-11 by (1.33%) indicating this proton was *cis*- to the isopropyl group.

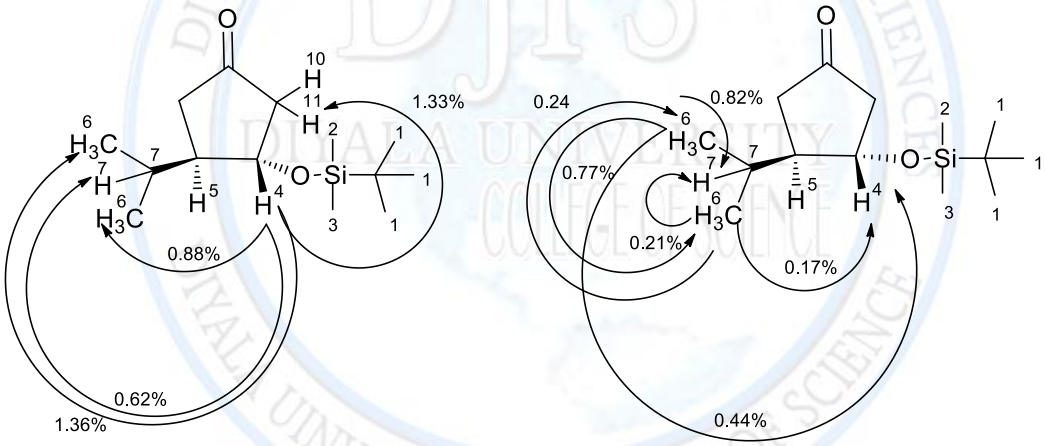


Figure 14.n.O.e enhancements for (384).

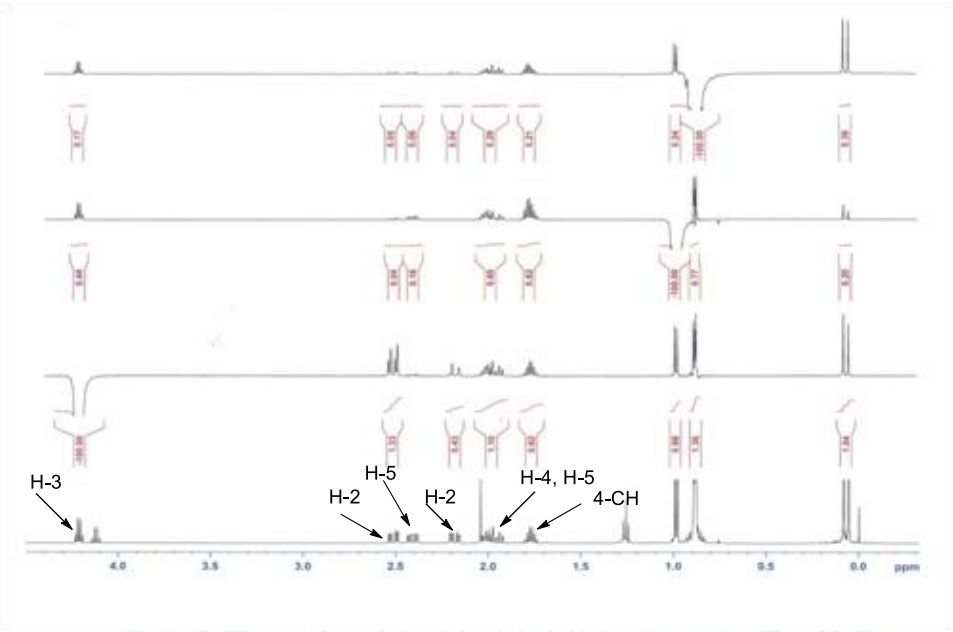


Figure 15.^{1}H NMR spectrum and n.O.e result of compound (384).

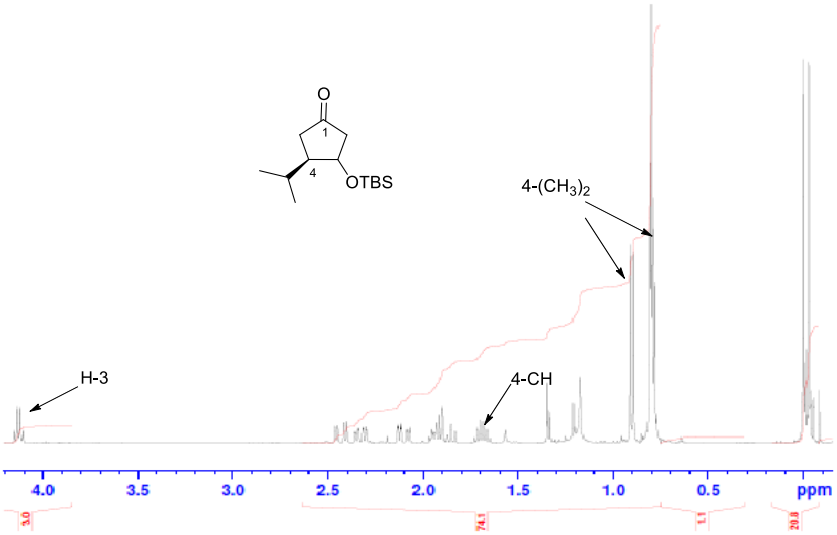


Figure 16.^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the compound (384).

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