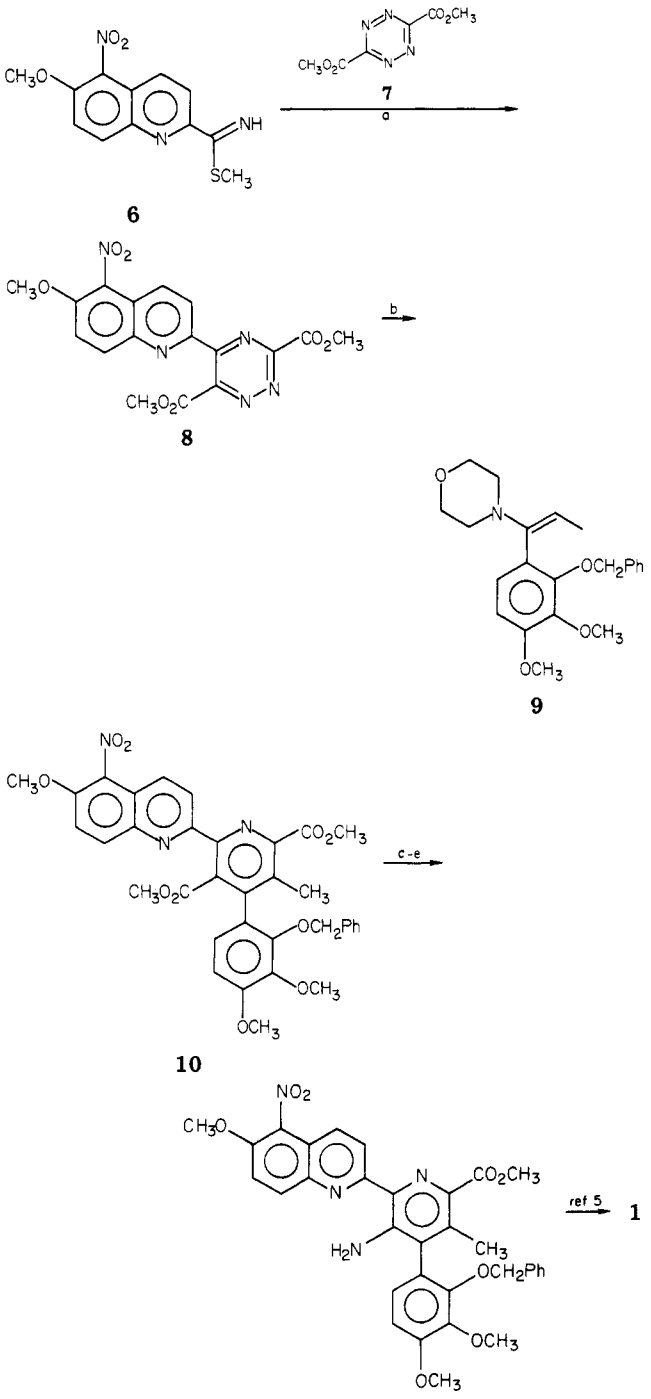
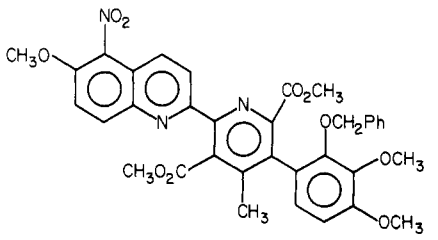
Scheme III[a]



[a] (a) dioxane, 80 °C, 24 h, 2.0 equiv of 7, 72%; (b) see Table I. (c) 12.0 equiv of PhSeNa, THF-HMPA, 70 °C, 36 h; CH_3OH, HCl cat., 25 °C, 18-22 h; (d) 5.0 equiv of $(PhO)_2P(O)N_3$, benzene, reflux, 2.5 h; H_2O, reflux, 2.5 h; (e) excess CH_3I, K_2CO_3, THF, 65 °C, 22 h, 16% from 10.

results in Table I indicate a clear trend, illustrating that the vigorous reaction conditions required for complete reaction eliminate the observed regioselectivity and as such the choice of reaction conditions[13] can determine the relative amount of 11.



11

Thus, the successive implementation of two inverse electron demand Diels-Alder reactions of heterocyclic azadienes provided the basis for a simple, convergent formal total synthesis of streptonigrin (1). A continued study of the factors governing the mode and regioselectivity of the cycloaddition reactions of 1,2,4-triazines, efforts to improve this approach to streptonigrin (1), and extension of this methodology to the synthesis of related antitumor antibiotics will be reported in due course.

Acknowledgment. This work was assisted financially by a Biomedical Research Grant (RR 5606), the University of Kansas General Research Allocation No. 3244-X0-0038, the National Institutes of Health (CA33668-01), and the Chicago Community Trust Co./Searle Scholars Fund. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for funds used in the purchase of equipment. We thank Professor A. S. Kende for spectra of authentic **10**, for a comparison sample of **12**, and for helpful discussions.

Registry No. 1, 3930-19-6; 2, 5263-87-6; 3, 5467-79-8; 4, 83220-09-1; 5, 83220-10-4; 6, 83220-11-5; 7, 2166-14-5; 8, 83220-12-6; 9, 83220-13-7; 10, 83220-14-8; 11, 83220-15-9.

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N-Acyl-β-enamino Ketones: Versatile Heterocyclic Synthons[1]

Summary: *N*-Acyl-β-enamino ketones are readily prepared from the potassium enolates of methyl ketones and diethyl *N*-(substituted)dithiocarbonimidates in tetrahydrofuran at room temperature; use of the corresponding isothiourea allows introduction of an NEt_2 substituent into the 3-position of the enamino ketone. 1,3-Oxazinium and 1,3-thiazinium salts are readily formed from these *N*-acyl-β-enamino ketones on treatment with 70% $HClO_4$ in Ac_2O or CF_3SO_3H.

Sir: In recent papers[2] a versatile synthesis of functionalized 1,5-enediones and their application in pyridine syntheses were described. We now report an equally versatile route to their nitrogen-containing analogues, *N*-acyl-β-enamino ketones, and the application of these enamino ketones in the synthesis of functionalized six-membered heterocyclic systems such as 1,3-oxazinium and 1,3-thiazinium salts. *N*-Acyl-β-enamino ketones have been

(13) All attempts to catalyze the cycloaddition reaction of 8 with 9 by the addition of conventional Lewis acid catalysts ($AlCl_3$, BF_3·OEt_2, anhydrous $FeCl_3$, $Cu(BF_4)_2$, $Cu(AcAc)_2$, $Co(AcAc)_2$, and $Ni(AcAc)_2$) lead to decomposition of enamine 9.

(14) Chicago Community Trust Co./Searle Scholar recipient, 1981-1985.

(1) (a) Partial support of this work by NSF Grant CHE 79-01704 is gratefully acknowledged. (b) Abstracted in part from the Ph.D. thesis of G.R.T. (1980).

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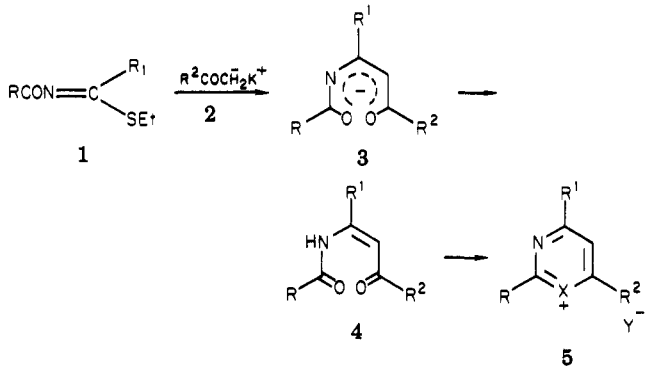
0022-3263/83/1948-0623$01.50/0

Table I. *N*-Acyl-β-enamino Ketones 4

R	R^1	R^2	mp, °C	yield, %	$M^{+\cdot}$ (% rel intens)	ν_{CO} (KBr), cm^{-1}
2,5-$Cl_2C_6H_3$	SEt	4-$CH_3OC_6H_4$	157-159	64	409 (5)	1675, 1600
2,5-$Cl_2C_6H_3$	SEt	2-C_4H_3S	142-143	88	385 (7)	1670, 1580
2-C_4H_3O	SEt	C_6H_5	127-130	78	301 (15)	1660, 1590
2,5-$Cl_2C_6H_3$	NEt_2	C_6H_5	120-122	68	390 (24)	1680, 1600
2,5-$Cl_2C_6H_3$	NEt_2	2-C_4H_3S[a]	141-143	48	396 (24)	1680, 1600

[a] From 4 (R^1 = SEt) and $HNEt_2$.



made in moderate yields from tris(acylamino)methanes and active methylene compounds[3] or by the hydrolysis of 1,3-oxazinium salts.[4] This present method has the marked advantage over these procedures of allowing considerable variation in the 1,5 aromatic substituents as well as at the 3-position and making these reactive intermediates readily available in good yields.

Reaction of diethyl *N*-(substituted)dithiocarbonimidates 1, prepared from dithiocarbamates by S-ethylation,[5] with the potassium enolate of a variety of methyl ketones 2 in tetrahydrofuran (THF) at room temperature gave the *N*-acyl-β-enamino ketones 4 described in Table I in moderate to excellent yields.[6] Use of 2 equiv of potassium *tert*-butoxide in the reaction suppressed side reactions by generation of the intermediate salt 3 and also facilitated isolation of 4. Thus, from diethyl *N*-(2,5-dichlorobenzoyl)dithiocarbonimidate (1; R = 2,5-$Cl_2C_6H_3$; R^1 = SEt; 5.0 g, 15.6 mmol) added to a solution of 2-acetylthiophene (2; R^2 = 2-C_4H_3S; 1.97 g, 15.6 mmol) and potassium *tert*-butoxide (3.69 g, 32.8 mmol) in anhydrous THF (75 mL), after stirring at room temperature for ca. 8 h, was obtained a deep-yellow precipitate of the potassium salt 3 (R = 2,5-$Cl_2C_6H_3$; R^2 = 2-C_4H_3S; R^1 = SEt). The salt was separated and was then added to an ice-cold 2% acetic acid solution (150 mL), giving 4 (R = 2,5-$Cl_2C_6H_3$; R^2 = 2-C_4H_3S; R^1 = SEt), which crystallized from benzene as pale-yellow microneedles, mp 142–143 °C.

Introduction of a diethylamino substituent into the 3-position of 4 is readily accomplished by use of the corresponding isothiourea 1 (R^1 = NEt_2). Thus 1 (R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2) and acetophenone under reaction conditions analogous to those above gave 4 (R = 2,5-$Cl_2C_6H_3$; R^2 = C_6H_5; R^1 = NEt_2) as tan microneedles, mp 120–122 °C (Table I). Alternatively, the SEt substituent in 4 can be displaced by diethylamine (100 °C in a sealed tube, 24 h) as in the formation of 4 (R = 2,5-$Cl_2C_6H_3$; R^2 = 2-C_4H_3S; R^1 = NEt_2) as fluffy, golden microneedles, mp 141–143 °C, from 4 (R = 2,5-$Cl_2C_6H_3$; R^2 = 2-C_4H_3S; R^1 = SEt). Table I illustrates the variety of substituents that may be introduced into 4 by these reactions.

The *N*-acyl-β-enamino ketones 4 underwent ring closure to the 1,3-oxazinium salts 5 (X = O) on treatment with 70% $HClO_4$ in Ac_2O at room temperature for several hours. Ring closure of 4 occurred most readily when R^1 = NEt_2, the corresponding reaction with 4 (R^1 = SEt), giving oxazinium salts characterized by spectral data but which underwent ready hydrolysis during purification procedures. Trifluoromethanesulfonic acid also effected ready ring closure of 4 (R^1 = NEt_2) in acetic anhydride solution at room temperature. Thus 2-(2,5-dichlorophenyl)-4-(diethylamino)-6-phenyl-1,3-oxazinium perchlorate (5; X = O; R = 2,5-$Cl_2C_6H_3$; R^2 = C_6H_5; R^1 = NEt_2; Y = ClO_4) was obtained from the correspondingly substituted 4 (0.30 g, 0.77 mmol) in Ac_2O (15 mL) and 70% $HClO_4$ (0.5 mL) after stirring at room temperature for 1 h. The oxazinium salt that separated crystallized from Ac_2O as colorless, irregular prisms, mp 236–238 °C [93%; ν_{CO} (KBr) 1635 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6, 1:1) δ 8.3–7.7 (m, 9, aromatic), 4.2 (q, 4, NCH_2), 1.5 (t, 6, CH_3)]. The corresponding trifluoromethanesulfonate, obtained by using trifluoromethane sulfonic acid as the cyclization acid in Ac_2O at room temperature, crystallized from 1,2-dichloroethane as colorless plates, mp 226–228 °C.

The above 1,3-oxazinium salts on treatment with Na_2S in dry acetone at room temperature afforded the yellow *N*-acyl-β-enamino thioketone, which when treated with $HClO_4$ in Ac_2O gave the corresponding 1,3-thiazinium salt 5 (X = S; R = 2,5-$Cl_2C_6H_3$; R^2 = C_6H_5; R^1 = NEt_2; Y = ClO_4). This crystallized from Ac_2O as golden, irregular prisms, mp 251–254 °C [68%; $\nu_{C=S}$ (KBr) 1635 cm^{-1}; NMR ($CDCl_3$–Me_2SO-d_6, 3:1) δ 8.3–7.6 (m, 9, aromatic), 4.2 (q, 4, NCH_2), 1.4 (m, 6, CH_3)].

The diversity of substituents that may be introduced into the 2-, 4-, and 6-positions and the high yields obtained in the conversions make this an attractive route to 1,3-oxa- and 1,3-thiazinium salts,[4,7] which are useful substrates for conversion into other heterocyclic systems.[7,8]

Registry No. 1 (R = 2,5-$Cl_2C_6H_3$; R^1 = SEt), 84433-58-9; 1 (R = 2-C_4H_3O; R^1 = SEt), 84433-59-0; 1 (R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2), 84433-60-3; 2 (R^2 = 4-$CH_3OC_6H_4$), 84433-61-4; 2 (R^2 = 2-C_4H_3S), 84433-62-5; 2 (R^2 = C_6H_5), 59175-43-8; 3 (R = 2,5-$Cl_2C_6H_3$; R^1 = SEt; R^2 = 4-$CH_3OC_6H_4$)·K, 84433-63-6; 3 (R = 2,5-$Cl_2C_6H_3$; R^1 = SEt; R^2 = 2-C_4H_3S)·K, 84433-64-7; 3 (R = 2-C_4H_3O; R^1 = SEt; R^2 = C_6H_5)·K, 84433-65-8; 3 (R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2; R^2 = C_6H_5)·K, 84433-66-9; 3 (R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2; R^2 = 2-C_4H_3S)·K, 84433-67-0; 4 (R = 2,5-$Cl_2C_6H_3$; R^1 = SEt; R^2 = 4-$CH_3OC_6H_4$), 84433-68-1; 4 (R = 2,5-$Cl_2C_6H_3$; R^1 = SEt; R^2 = 2-C_4H_3S), 84454-23-9; 4 (R = 2-C_4H_3O; R^1 = SEt; R^2 = C_6H_5), 84454-24-0; 4 (R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2; R^2 = C_6H_5), 84454-25-1; 4 (R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2; R^2 = 2-C_4H_3S), 84454-26-2; 5 (X

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= O; R = 2,5-$Cl_2C_6H_3$; R^1 = SEt; R^2 = 4-$CH_3OC_6H_4$; Y = ClO_4), 84433-70-5; **5** (X = O; R = 2,5-$Cl_2C_6H_3$; R^1 = SEt; R^2 = 2-C_4H_3S; Y = ClO_4), 84433-72-7; **5** (X = O; R = 2-C_4H_3O; R^1 = SEt; R^2 = C_6H_5; Y = ClO_4), 84433-74-9; **5** (X = O; R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2; R^2 = C_6H_5; Y = ClO_4), 84433-76-1; **5** (X = O; R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2; R^2 = 2-C_4H_3S; Y = ClO_4), 84433-78-3; **5** (X = O; R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2; R^2 = C_6H_5; Y = trifluoromethanesulfonate), 84433-79-4; **5** (X = S; R = 2,5-$Cl_2C_6H_3$; R^1 = NEt_2; R^2 = C_6H_5; Y = ClO_4), 84433-81-8.

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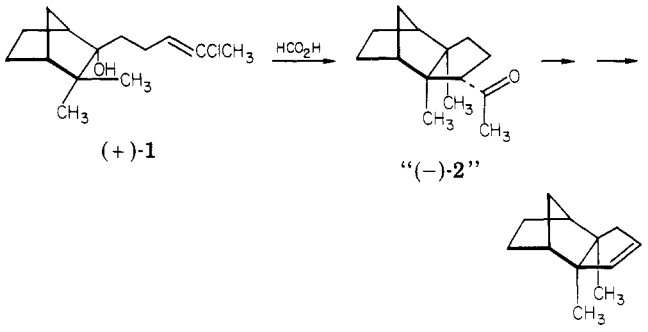
Absolute Stereochemistry of (-)-Albene

Summary: Stereochemical correlations between a synthetic precursor to the natural product albene and β-santalene have led to a reassignment of absolute stereochemistry: (-)-albene is (1*S*,2*S*,6*S*,7*R*)-2,6-dimethyltricyclo-[5.2.1.$0^{2,6}$]dec-3-ene. Earlier work that reached an opposite stereochemical conclusion assumed an endo 3,2 methyl shift in a 2-norbornyl cation: that mode of rearrangement must now be discounted.

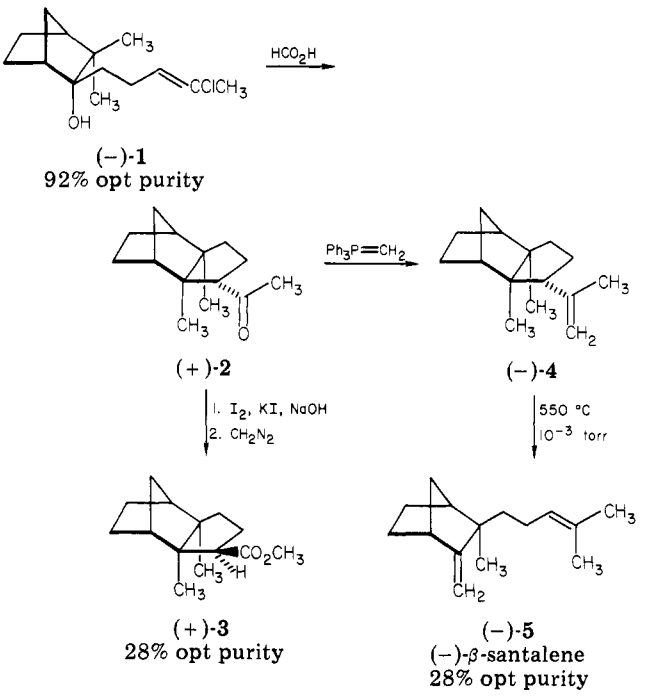
Sir: Albene, a naturally occurring hydrocarbon first isolated in 1962,[1] is 2-*endo*,6-*endo*-dimethyltricyclo-[5.2.1.$0^{2,6}$]dec-3-ene.[2] A key step in the sequence of reactions leading from (+)-camphenilone to (-)-albene, a chloro olefin annelation[3-5] converting alcohol (+)-**1** to a ketone formulated as "(-)-**2**", was viewed[2] as the first example of an endo 3,2 alkyl shift in a Nametkin rearrangement.[6] In accord with this interpretation, (-)-albene was assigned the 1*R*,2*R*,6*R*,7*S* absolute stereochemistry.[2]



An interest in albene[7] and in the several mechanistic and stereochemical issues posed by the reported conversion of (+)-**1** to "(-)-**2**" led to the present independent determination of the absolute stereochemistry of (-)-albene.

(-)-Camphenilone of 92% optical purity[8] and 1-lithio-4-chloropent-3-ene[9] gave carbinol (-)-**1** (Scheme I) in 76% yield.[10] Conversion of this intermediate to ketone (+)-**2** under the conditions utilized by earlier workers[2,4,5] was accomplished in 75% yield.[11] The optical purity of (+)-**2** was determined indirectly: methyl ester (+)-**3**,[12,13] $[\alpha]_{546}$ +10.5° (*c* 1.12, $CHCl_3$), secured from (+)-**2** through a haloform reaction[14] and esterification of the acid product with diazomethane, was analyzed by NMR spectroscopy in the presence of the chiral shift reagent Eu(hfbc)$_3$ and found to be 28% optically pure. Considerable racemization, then, accompanied the annelation in formic acid.

Scheme I



Wittig reaction between ketone (+)-**2** and methylenetriphenylphosphorane in dimethyl sulfoxide[15] gave olefin (-)-**4** (88% yield).[16] Under conditions of flash vacuum pyrolysis (550 °C, 10^{-3} torr) olefin (-)-**4** was partially converted to β-santalene through a retroene reaction.[17] The β-santalene product[18] showed $[\alpha]_{546}$ -36.8° (*c* 0.81,

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(10) The physical properties, and NMR and IR spectral characteristics, of (-)-**1** (and of (+)-**2**) matched previously reported values;[2] (-)-**1** had $[\alpha]_{546}$ -16.3° (*c* 5.05, $CHCl_3$) (lit.[2] $[\alpha]_D$ +16.2° for (+)-**1**).
(11) $[\alpha]_{546}$ +34.9° (*c* 3.43, $CHCl_3$) (lit.[2] $[\alpha]_D$ -17.5° for (-)-**2**).
(12) NMR ($CDCl_3$) δ 3.69 (s, 3 H), 2.60 (dd, *J* = 9, 9 Hz, 1 H), 2.19 (br s, 1 H), 0.90-1.90 (c, 11 H), 0.88 (s, 3 H), 0.73 (s, 3 H); IR 2990, 2950, 2870, 1730, 1470, 1440, 1240, 1205, 1175 cm^{-1}. Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.64; H, 9.97. Found: C 75.58; H, 9.78.
(13) The stereochemistry of the carboxylate function was assigned after observing the chemical shifts of the C(2,6)-methyl groups in the presence of increasing proportions of Eu(hfbc)$_3$.
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(16) NMR ($CDCl_3$) δ 4.78 (br s, 1 H), 4.64 (br s, 1 H), 1.74 (s, 3 H), 0.90-2.40 (c, 13 H), 0.83 (s, 3 H), 0.61 (s, 3 H); IR 3090, 2990, 2940, 2870, 1645, 1470, 1450, 1385, 1375 cm^{-1}. Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.87; H, 11.94. $[\alpha]_{546}$ -3.33° (*c* 1.70, $CHCl_3$).
(17) β-Santalene produced in this fashion had the following: NMR ($CDCl_3$) δ 5.08 (br t, *J* = 7 Hz, 1 H), 4.71 (s, 1 H), 4.44 (s, 1 H), 2.64 (br s, 1 H), 2.10 (br s, 1 H), 0.80-2.05 (c, 10 H), 1.67 (s, 3 H), 1.61 (s, 3 H), 1.04 (s, 3 H); IR 3150, 3060, 2960, 2920, 2870, 1650, 1455, 1375, 1355 cm^{-1}; mass spectrum, *m/e* 204 (M^+), 189, 176, 161, 147, 121, 94 (base); high-resolution MS M^+ obsd 204.1872, $C_{15}H_{24}$ requires 204.1878 [lit.[18] NMR (CCl_4) δ 5.0 (br, 1 H), 4.68 (s, 1 H), 4.40 (s, 1 H), 1.64 (s, 3 H), 1.57 (s, 3 H), 1.03 (s, 3 H)].
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