Synthetic studies towards bruceantin. Part 1. Establishment of the carbon network

SULTAN DARVESH, ANDREW S. GRANT, DAVID I. MAGEE, AND ZDENEK VALENTA[1]
Department of Chemistry, University of New Brunswick, Fredericton, N.B., Canada E3B 6E2

Received September 20, 1990

SULTAN DARVESH, ANDREW S. GRANT, DAVID I. MAGEE, and ZDENEK VALENTA. Can. J. Chem. **69**, 712 (1991).

In a synthetic approach to the biologically active quassinoid bruceantin **1**, intermediate **47** was prepared, which contains all required C-atoms, rings A and B, and four of the 10 chiral centers of bruceantin. The possibilities for a convergent strategy were explored, in which a 5-carbon unit would be joined to a 15-carbon unit by three bonds. After the study of various alkylations and Michael additions needed for the key step, it was found that 3-iodo-1-trimethylsilyl-5-hexenyne **44** adds to the dianion of methyl ketone nitriles **3** and **13** chemo-, diastereo-, and enantioselectively.

Key words: bruceantin, quassinoids, alkylation, Michael addition.

SULTAN DARVESH, ANDREW S. GRANT, DAVID I. MAGEE et ZDENEK VALENTA. Can. J. Chem. **69**, 712 (1991).

Dans une approche à la synthèse de la quassinoïde brucéantine (**1**) biologiquement active, on a préparé l'intermédiaire **47** qui contient tous les atomes de carbone requis, les cycles A et B ainsi que quatre des 10 centres chiraux de la brucéantine. On a exploré les possibilités de stratégie convergente dans lesquelles une unité de cinq atomes de carbone serait reliée à une unité de 15 atomes de carbone par trois liaisons. Après avoir étudié diverses alkylations et additions de Michael requises pour l'étape clé, on a trouvé que le 3-iodo-1-triméthylsilyl-hexén-5-yne (**44**) s'additionne aux dianions des méthylcétone-nitriles **3** et **13** d'une façon chémo-, diastéréo- et énantio-sélective.

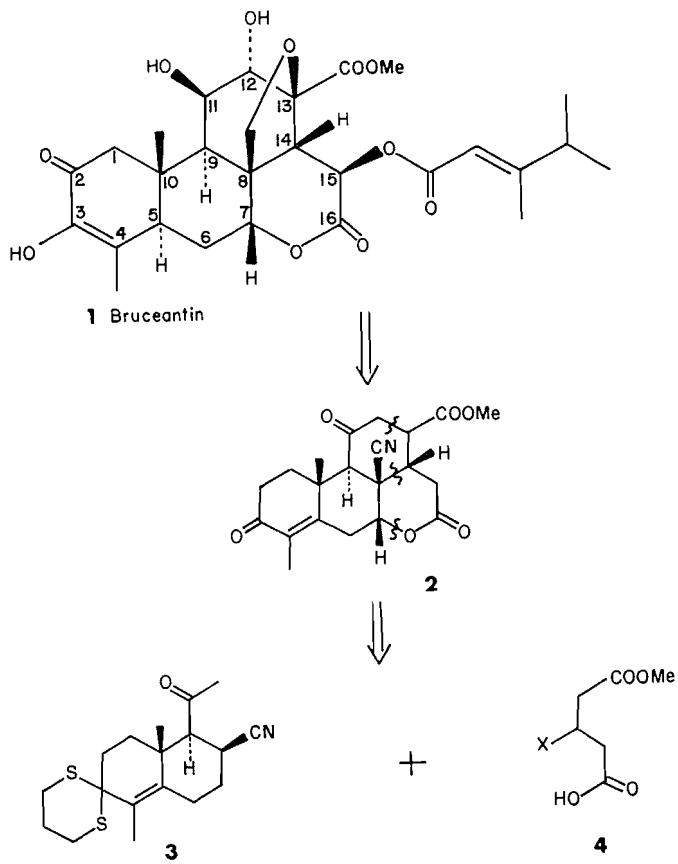
Mots clés : brucéantine, quassinoïdes, alkylation, addition de Michael.

[Traduit par la rédaction]

The last two decades have seen the *Simaroubaceae* family of the plant kingdom make a prominent mark in natural product chemistry. The bitter substances produced in plants of this family, known as the quassinoids (1, 2), have received increased attention with the finding that some of them possess strong antileukemic activity in the murine lymphocytic leukemia P-388 test system, in addition to antimalarial, amebicidal, and antiviral activities.

The wealth of information gathered in the last two decades has shown what structural features are required for the antineoplastic activity exhibited by the quassinoids (3). An A-ring enone function, a C6 or a C15 ester function, and an oxymethylene bridge between C8 and C11 or C13 are essential for optimal activity. Due to this functional and stereochemical complexity, coupled with the potential use in cancer and other therapies, a considerable amount of synthetic activity has been expended towards these compounds (4). Four tetracyclic members of the C20 picrasane family have been synthesized, all in racemic form (5), and just recently an enantioselective synthesis has been reported for three others (4*a*). Finally, the synthesis of racemic 15-deoxybruceolide and a relay conversion of the naturally derived (−)-form of this compound into (−)-bruceantin **1** have been reported (4*h*). From the scarcity of completed syntheses, it is evident that much work is still required in this area, especially on the design of an efficient general synthesis. We wish to report in full our work on the synthesis of the natural quassinoid bruceantin **1**.

Bruceantin contains 10 asymmetric carbon atoms, of which six are at the junctions of the three carbon rings and the lactone ring. Our strategy, therefore, consisted first of the formation of the skeleton with the proper relative stereochemistry, followed by the subsequent incorporation of the functional groups with the desired configuration (Scheme 1). It appeared to us that disconnection at the lactone ether oxygen, at C8 and at C12, would present two "relatively simple" halves. This convergent strategy, we felt, held great promise since the connection of these two halves could be achieved in any one of several possible sequences (Fig. 1, where the three arrows point towards the potential electrophilic centers).



SCHEME 1

Results and discussion

Our synthetic route to bicyclic ketone **3**, depicted in Scheme 2, was initiated by the reaction of 2-methyl-1,3-cyclohexane dione with ethyl vinyl ketone under basic conditions to yield the Michael adduct **7**. This compound was then directly subjected,

[1]Author to whom correspondence may be addressed.

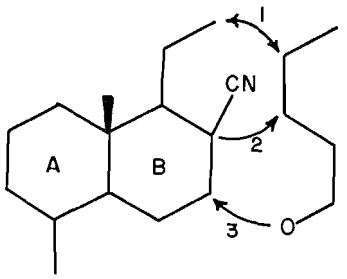
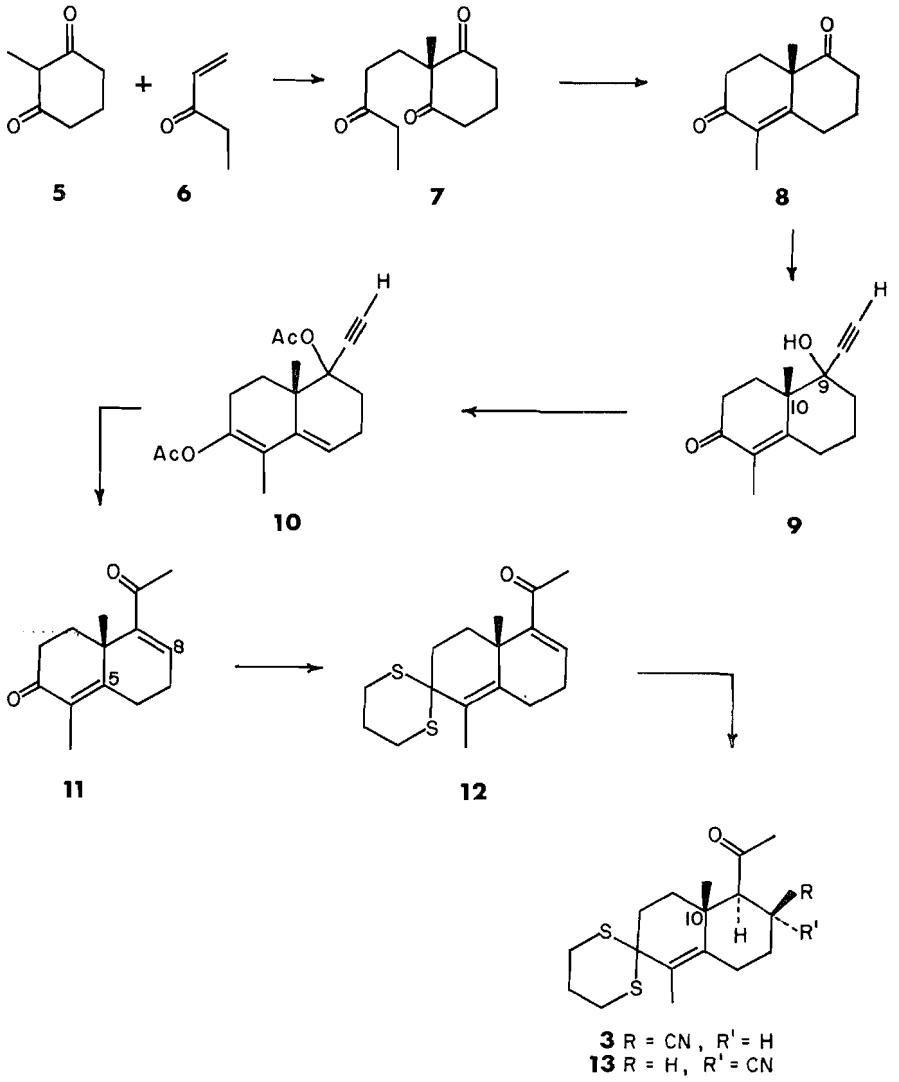


FIG. 1. Potential connecting points of the "two halves" for the synthesis of bruceantin.

without any purification, to pyrrolidine in refluxing benzene with azeotropic removal of water to furnish the enedione **8** in 67% overall yield (6). Ethynylation of **8** with lithium acetylide in liquid ammonia (*7a*) at −78°C proceeded smoothly and regioselectively to furnish the carbinol **9** in 71% yield. Treatment with acetic anhydride and a catalytic amount of *p*-toluenesulfonic acid (pTSA) (*7a*) resulted in clean conversion to the diacetate **10** in 94% yield. As Newman *et al.* (*7a*) found in a similar case, the transformation of the ethynyl carbinol to the diacetate became necessary due to the juxtaposition of the enone and the hydroxyl group in **9**. The acidic conditions and high temperatures required to produce the α,β-unsaturated acetyl group of **11** led to considerable destruction of the starting material when the direct **9** → **11** conversion was attempted. This was undoubtedly due to a reverse aldol process, which fragmented the C9—C10 bond. With the tertiary alcohol now protected, the Rupe rearrangement (*7a*, *7b*) proceeded as expected on treatment with refluxing formic acid (90%) for 2 h to produce the diene dione **11** in 70% yield as a crystalline solid. The remaining task was the installation of the nitrile at C8. We assumed that a regioselective hydrocyanation could be accomplished since C8 could be expected to be much less hindered than the corresponding C5 position. However, the best conditions found, sodium cyanide in dimethyl formamide (DMF) in the presence of sodium bicarbonate, led to a 1:1 mixture of regioisomers, and in only 40% conversion. To circumvent this problem, diene dione **11** was first treated with 1,3-propane dithiol and $BF_3 \cdot OEt_2$ in Et_2O to produce the protected enone **12** in 72% yield. Compound **12** then smoothly reacted with aqueous potassium cyanide in ammonium chloride buffered DMF to produce the epimeric nitriles **3** and **13** in a combined yield of 77%. The



SCHEME 2

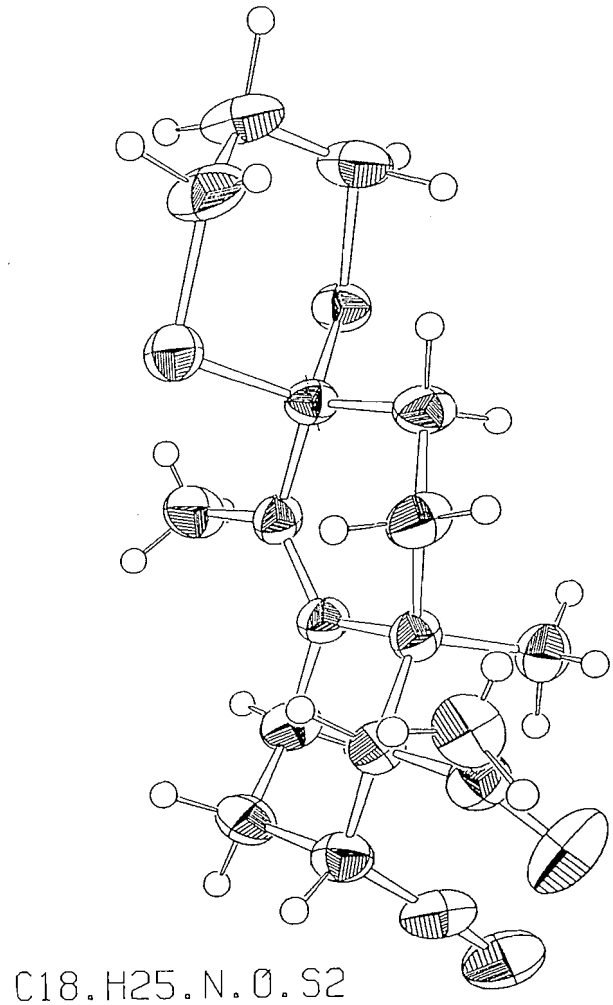


FIG. 2. X-ray structure of nitrile **3**.

typical ratio of nitriles was 5:1 in favor of **3**; however, there were instances when the other epimer predominated. The reasons for this variability are unclear.

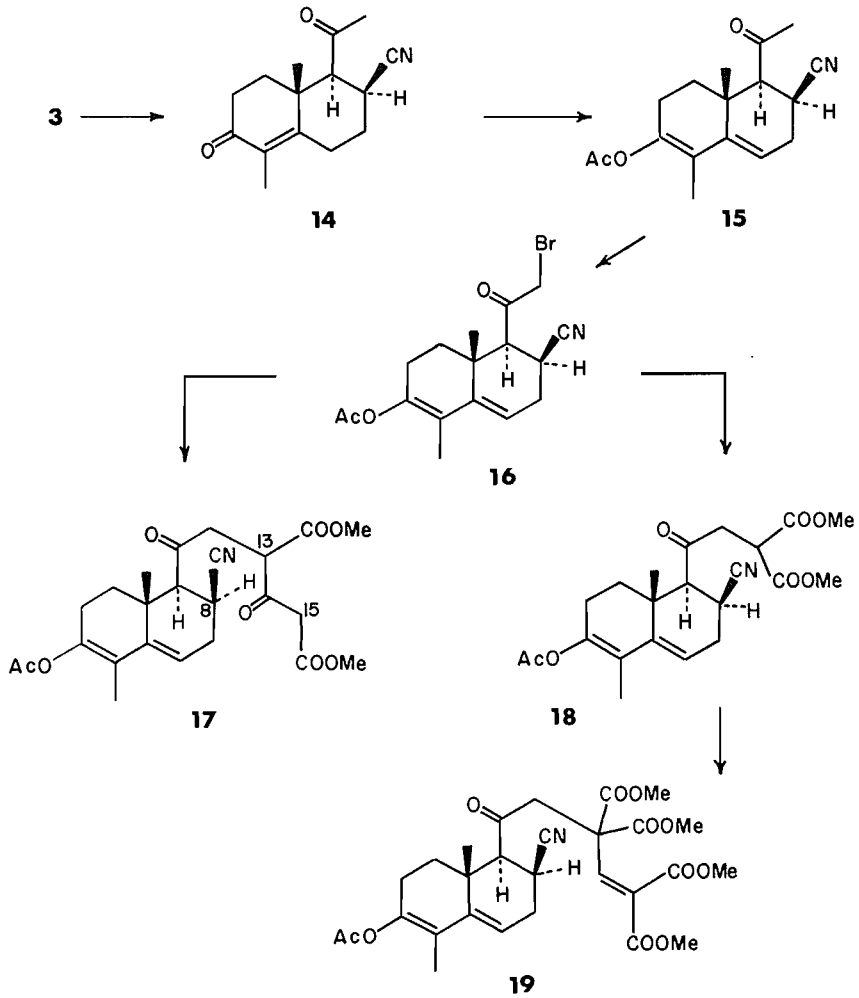
The structures of **3** and **13** were initially assigned as shown on ^{1}H NMR evidence. Epimer **3** showed a singlet at δ 1.47 for the C10 methyl group, while in **13** it appeared at δ 1.10. The difference in chemical shift was attributed to the fact that the C10 methyl group in **3** was deshielded by the nitrile. This assignment was later substantiated by single crystal X-ray crystallography (Fig. 2). From Fig. 2, it can be seen that the nitrile is in a quasi-axial position, while the acetyl group occupies the equatorial position. It was assumed, and later shown by chemical transformation, that both the acetyl group and the nitrile were equatorially disposed in nitrile **13**.

The next objective was to attach a suitable side chain, which would contain the remaining carbons required for the construction of the skeleton of bruceantin. Based on previous work done in these laboratories on the synthesis of 14β-hydroxysteroids (8), it was assumed that the best assembly sequence would be to form the C12—C13 bond first, followed by the C8—C14 bond (Fig. 1, arrows 1 and 2). In particular, this approach was expected to provide the desired stereochemistry at the quaternary C8 carbon.

Investigation of this strategy (Scheme 3) began by treating nitrile **3** with *N*-chlorosuccinimide and silver carbonate in aqueous acetonitrile (9) to give enone **14** in 80% yield. This was then simply protected as its dienol acetate **15** by treatment with acetic anhydride and a catalytic amount of hydrobromic acid (87% yield). Complete chemoselective bromination of C12 was accomplished with phenyl trimethyl ammonium perbromide (10) in tetrahydrofuran (THF) to give the unstable bromo ketone **16**. This bromo derivative became the pivotal point of further investigations in which C12 was used as an electrophilic center. Due to the instability of this compound, it was always used immediately after preparation. Bromide **16** was treated with the sodium salt of dimethyl acetone dicarboxylate to furnish diester **17** in 52% overall yield. Theoretically, this product could exist in eight different forms: the two diastereoisomers at C13, two geometrical isomers of the enol towards C12, and four isomers of the enol towards C15 (*E*/*Z* and diastereoisomers at C13). Three of these eight possible states were observed in the 200 MHz NMR spectrum, with the ratio of keto:enol forms being approximately 3:2. All the carbons required for the bruceantin skeleton were now present, and an aldol reaction between C8 and C14 would deliver the last crucial bond.

Before this aldol reaction could be accomplished, however, an obvious acidity problem had to be overcome. It was assumed that extending conjugation into ring B would give the C8 hydrogen an acidity comparable to those of H-atoms in the side chain. To meet this objective, direct bromination, via a variety of methods, was attempted on dienol acetate **17**, but only significant loss of starting material with no detection of the desired product was observed in all cases. These problems were attributed to the presumed high reactivity of the enol groups present in the side chain. All attempts to overcome these difficulties by conversion into a β-haloglutaconate or an enol acetate failed. Thus, unfortunately, compound **17** had to be discarded as a potential synthetic intermediate, in spite of its initially highly promising distribution of functional groups.

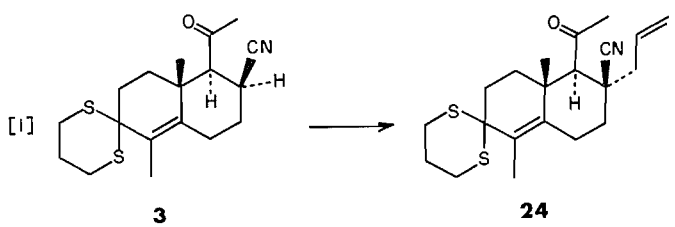
It was next attempted to remove the problem by incorporating a side chain that contained no acidic protons. Direct conversion of bromo acetate **16** to the malonyl adduct **18** proceeded uneventfully in 68% yield upon treatment with the sodium salt of dimethyl malonate. The sodium enolate of **18** was then quenched with chloromethylene malonate to yield the tetraester **19** in 75% yield. This compound now contained only the acidic protons at C9, C12, and C8, none in the added side chain. However, when tetraester **19** was treated with sodium hydroxide in the UV tube, it exhibited an unusual bathochromic shift to 400 nm. After inspection of the ^{1}H NMR spectrum, this shift was attributed to the rearranged product **20** (Scheme 4), presumably formed by addition of the C12 anion to the reactive Michael acceptor to form a cyclopropane intermediate, which subsequently reopened to give the more stable malonyl anion. It was also found that, in previous reactions, significant amounts of rearrangement product **20** were formed when, for the preparation of **19**, excess sodium hydride was used in the initial anion formation of **18**. All attempts to alleviate this problem failed; these included reduction of the C11 ketone with sodium borohydride, L-Selectride, or lithium borohydride and the extension of ring-A conjugation via bromination/dehydrobromination or selenation/elimination. However, when malonyl adduct **18** was treated with phenyl selenenyl chloride in benzene in the presence of silver trifluoroacetate (11), selenide **21** was produced in 70% yield as a single isomer (Scheme 5), the stereochemistry of which was not determined. Selenide **21** was then transformed into the tetraester **22** as before in a moderate 47% yield. Oxidation with *m*-chloroperbenzoic acid in methylene chloride then led, unfortunately, to the tertiary allylic alcohol **23** in 80% yield



SCHEME 3

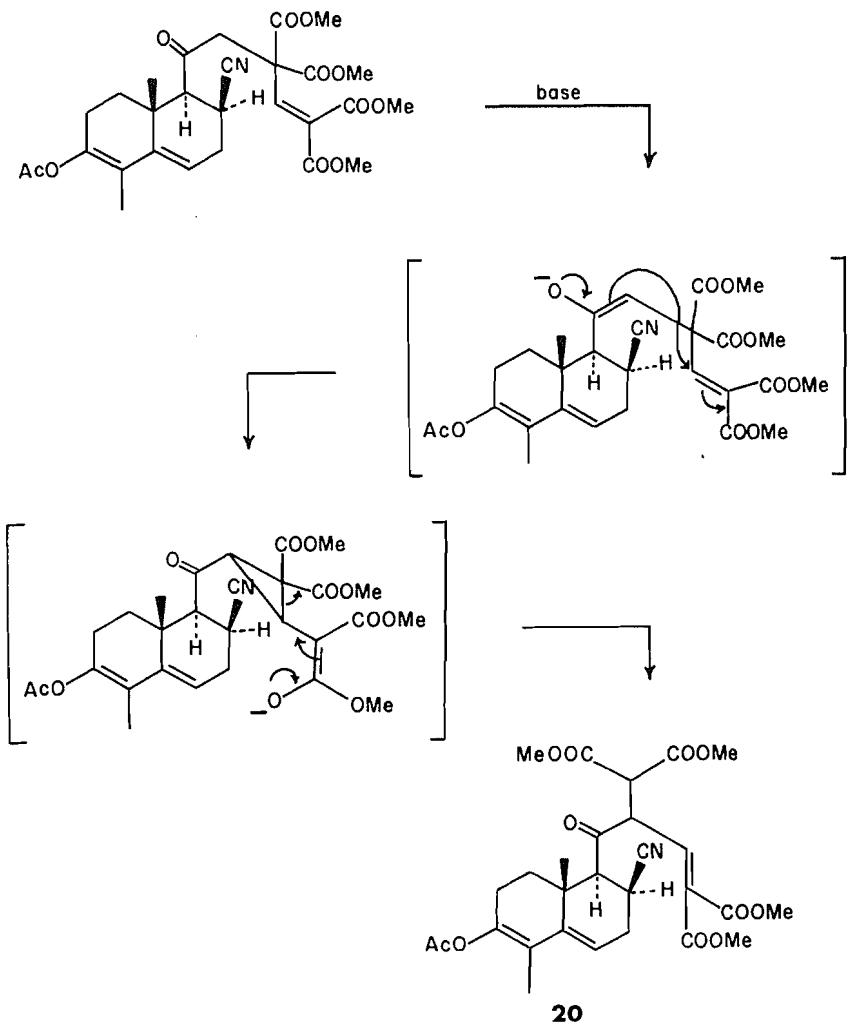
via the [2,3]-sigmatropic rearrangement of the selenoxide (12). Clearly, the presence of the C3 keto group did not usefully slow down the allylic selenoxide rearrangement. Even though this rearrangement is an equilibrium reaction, prolonged treatment had no effect on the product distribution.

It now became clear that an efficient continuation of the synthesis required that the five additional carbon atoms and the method for joining them be kept relatively simple. While investigating other avenues, we became intrigued with the following serendipitous result; treatment of **3** with five equivalents of lithium diisopropyl amide in THF at −78°C, followed by excess allyl bromide, gave **24** as the sole product in 88% yield (eq. [1]).



While it was not surprising that the alkylating agent approached the molecule at C8 exclusively from the α-face, it was indeed surprising that no alkylation was observed at the enolate carbon since we were undoubtedly dealing with a dianion. It must be assumed that the enolate anion alkylates very slowly, if at all, after the first alkylation occurs.

Utilization of this chemistry began with investigating the coupling of the dianion with several functionalized Michael acceptors (Table 1). Although two new asymmetric centers were created (three in the case of **33**, entry i), only one was of particular concern, C8; the C14 stereochemistry could be adjusted at a later stage. Several results listed in Table 1 are noteworthy. The reaction with ethylene malonate (entry a) gave the same chemo- and stereoselectivity at C8 as was observed for the alkylation with allyl bromide, but in poorer yield. Compound **26**, which was designed to incorporate the added oxygen functionality required in bruceantin, failed badly, even though it did give a product with the correct C8 stereochemistry. We concluded that the isopropylidene moiety of **26** was experiencing severe steric interactions with the decalin system, and that appropriate changes would overcome this. As seen in entry c, changing to an acetylene moiety did indeed improve the yield drastically; unfortunately, it also had a deleterious effect on the chemo- and stereoselectivity. The reason for the marked difference in reaction course is not at all evident, especially considering the fact that no reaction was observed for the di-*tert*-butyl derivative **28** (entry d). Other simple Michael acceptors were tried (entries e–h) but either no reaction or complex mixtures were obtained. The most interesting result was that with α-bromocrotonolactone (entry i). A single isomer was obtained in a reaction in which two new chiral centers were created by the Michael addition and a third one by enolate protonation. In



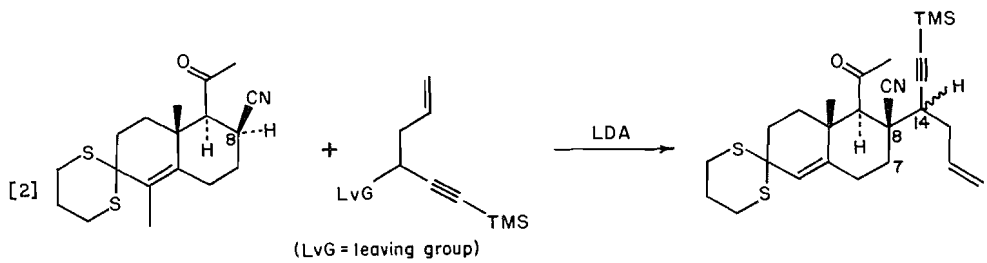
20

SCHEME 4

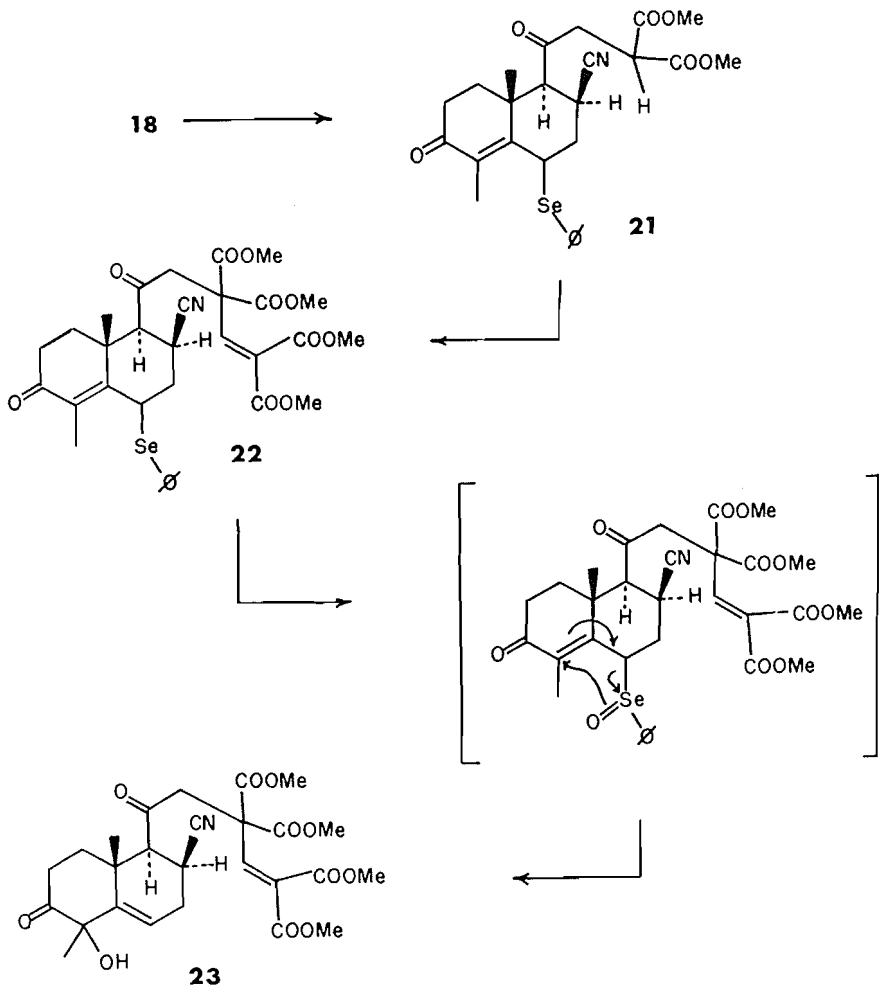
general, diastereoselective Michael reactions, in which two new chiral centers are generated, are not common. Reported cases include enamine and enolate additions to nitroolefins (13, 14).

The discouraging yields and selectivities in the Michael reactions forced us to consider "simple" alkyl halides, which would simulate the reactivity of allyl bromide but possess the required chain length and be functionalized enough to allow for further elaboration. After considerable experimentation, we decided to pursue haloenynes of type **38** as targets (eq. [2]). It should be noted that compounds **38** contain a chain of six carbons and that the double bond would therefore have to be cleaved at the appropriate time to give the desired chain length and terminal carboxylic acid functionality. Furthermore, the alkylation (eq. [2]) would only be efficient if, in addition to being chemoselective (attack at C8 rather than C12) and stereoselective at C8 (α-attack), it were also enantioselective (configuration at C14 of the product). Interestingly, however, *it should not matter which C14 diastereoisomer is formed*, as long as it is formed in high yield. Depending on the stereochemical outcome of the alkylation at C14, the acetylene would then be used either for the bond formation at C12 or at C7, while the other required bond (C7 or C12) would be formed using the allyl group. The C14 configuration of the alkylation product will thus dictate subsequent chemistry!

Our approach to the required compounds was initiated from the known aldehyde **39** (15), which was converted to propargylic alcohol **40** upon treatment with allyl magnesium bromide (Scheme 6). Mesylation under standard conditions gave **41**, which was then subjected to refluxing acetone with the appropriate potassium halide to give the corresponding chloride **42**,



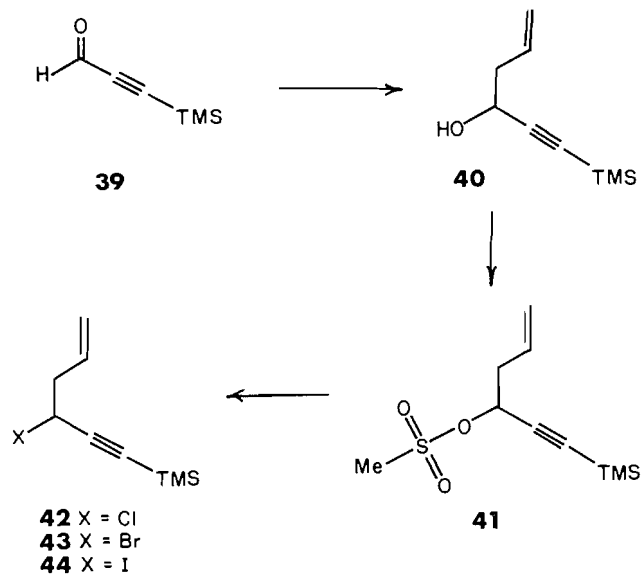
38



SCHEME 5

bromide **43**, and iodide **44** in 30–40% yield overall. With a convenient synthesis of these halides now in hand, the reactivity of each of them was investigated.

The dianions of nitriles **3** and **13** were generated by treatment with lithium pyrrolidide (LP)[2] in THF at −78°C for 2 h and then quenched with chloride **42** to give no alkylated product (Scheme 7). Upon recovery of the starting materials it was discovered that a significant quantity of the eliminated product **45** was obtained. This meant that the dianion, at least with this halide, acted as a base rather than a nucleophile. Treatment of the dianion, formed under identical conditions as before, with bromide **43** generated two new products, **46** and **47**, as a 1:1 mixture in 80% yield based on recovered starting material. These products arose from the two possible substitution pathways, namely S_N2 displacement to give **47** and S_N2' displacement to furnish **46**. Finally, treatment of the dianion with iodide **44** generated a single compound, **47**, in 95% yield and 50% conversion. Single crystal X-ray crystallography revealed that nitrile **47** possessed the correct C8 configuration and the indicated stereochemistry at C14 (Fig. 3). The enantioselectivity at C14 can possibly be explained by a transition state orientation of the two molecules indicated in Fig. 4. Placement of the acetylene under the decalin system and of the H-atom under the presumably strongly hindering ionic region would allow the more sterically demanding allyl



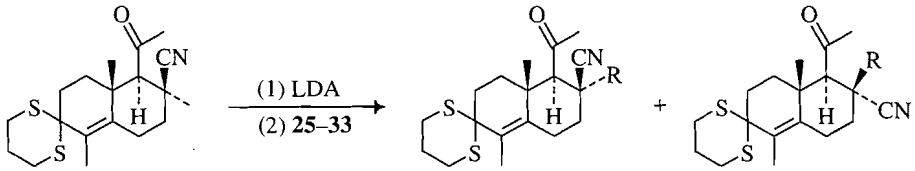
SCHEME 6

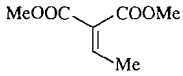
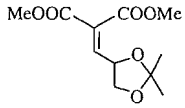
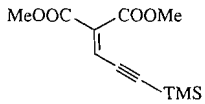
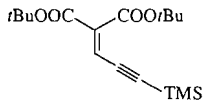
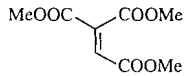
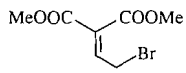
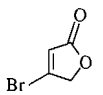
group to align itself away from the ring. This analysis not only rationalizes why the observed product is formed, but also why the process is so selective.[3]

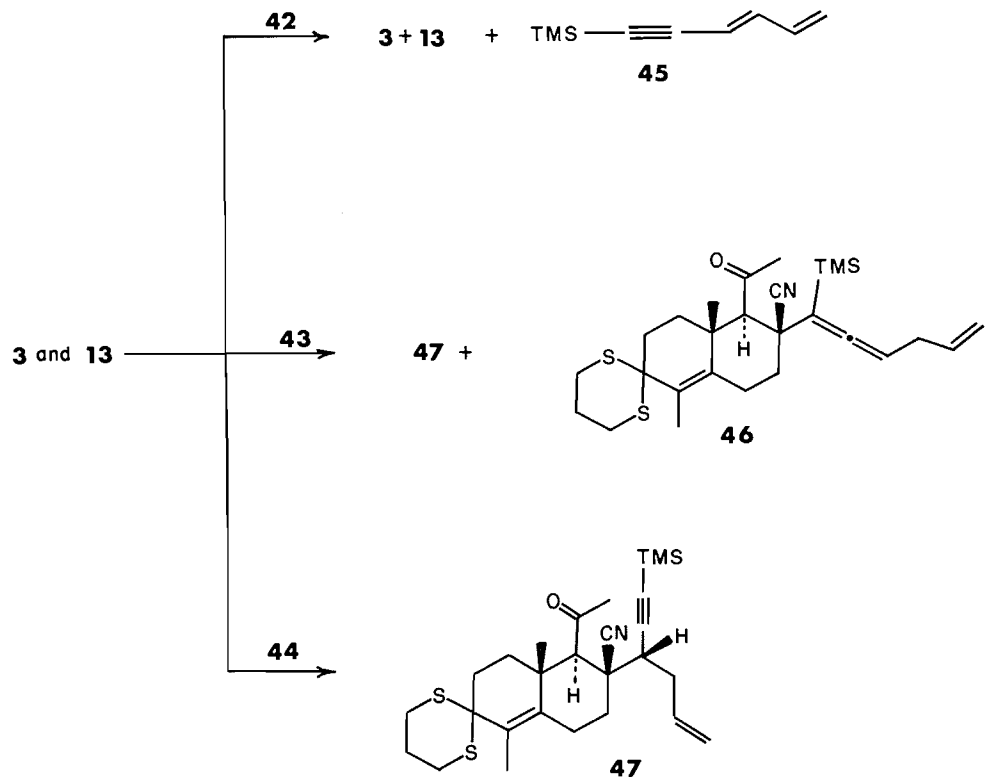
[2]It was found that the nitriles could be used without separation when LP was used as a base instead of LDA. We have no evidence that LP or pyrrolidine reacted with the halides **42**–**44** under the reaction conditions used.

[3]The proposed transition state geometry (Fig. 4) finds some support in the fact that the conformation of the side chain in **47** as determined crystallographically is very similar.

TABLE 1. Michael additions



	Michael acceptor	product yield (α/β)	Ratio of stereoisomers (at C14-H of side chain; determined by ^{1}H NMR)
		34–37α	**34–37β**
(a)	 **25**	**34** 49% (1/0)	2:1
(b)	 **26**	**35** 12% (1/0)	2:1
(c)	 **27**	**36** 77% (1/0) + C12 regioisomer	2:1
(d)	 **28**	No reaction	—
(e)	 **29**	Complex mixture	—
(f)	 **30**	Complex mixture	—
(g)	 **31**	No reaction	—
(h)	 **32**	No reaction	—
(i)	 **33**	**37** 20% (1/0)	Single isomer



SCHEME 7

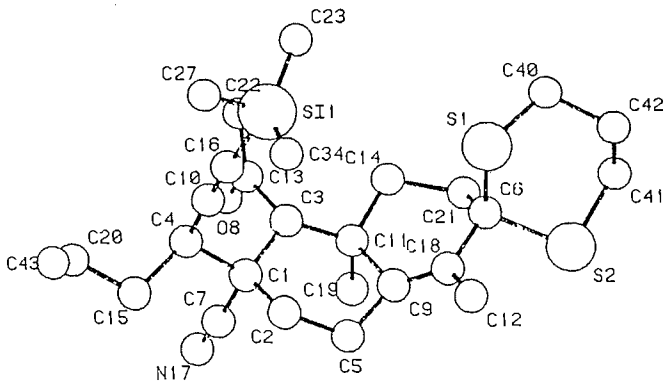


FIG. 3. X-ray structure of nitrile **47**.

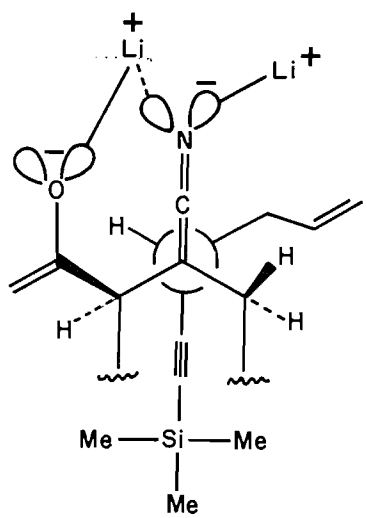


FIG. 4. Proposed transition state geometry of alkylation reaction.

Several attempts were made to improve the conversion of starting material. For example, HMPA was added (16), various concentrations of iodide **44** were used, and the temperature of the reaction was elevated, but no change was observed. This anomalous behavior has been observed in other alkylation systems (17). Regardless of the technical difficulties associated with only 50% conversion, the reaction was found to be high yielding, selective, and, most important, it provided the remaining carbon atoms required for the bruceantin skeleton in a simple yet differentiable form.

All compounds described here are racemic. Thus, in the alkylation reaction, each enantiomer of **3** (and **13**) selected the "fitting" enantiomer of racemic iodide **44**. Based on literature precedents (18), the formation of optically pure enedione **8** via an amino acid catalyzed aldol reaction of prochiral trione **7** will present no difficulties. It can then be anticipated that enantiomerically pure keto nitriles **3** and **13** thus prepared will react with only the fitting enantiomer of racemic iodide **44**. The nonreacting enantiomer of **44** will then either re-racemize by the action of the iodide ion generated in the alkylation reaction, or will be isolated and reconverted to the racemate in a separate reaction.

The next objective was to utilize alkylation product **47** for elaboration into compounds of type **2**. This work is reported in the following article.

Experimental section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin–Elmer IR spectrophotometer model 717B using sodium chloride cells (0.5 mm) and are reported in wave numbers (cm^{-1}) with polystyrene as standard. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-200 (200 MHz) or a Varian T60 (60 MHz) spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to tetramethylsilane as standard. Low resolution mass spectra were re-

corded on a Hitachi Perkin–Elmer RMU-6D spectrometer. High resolution mass spectra were recorded at the Mass Spectrometry Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta. Elemental analyses were performed at Guelph Chemical Laboratories Ltd., Guelph, Ontario. Ultraviolet (UV) spectra were recorded on a Beckman spectrophotometer model 25, using quartz cells (4.5 mL capacity).

All reactions, unless otherwise specified, were run under an inert atmosphere of Ar or N_2, and reactions requiring anhydrous conditions were performed in a flame-dried or oven-dried (120°C) apparatus. Temperatures below room temperature refer to bath temperatures. Solvents and anhydrous reagents were dried according to established procedures by distillation under N_2 from an appropriate drying agent (19).

Analytical TLC was performed on E. Merck precoated silica gel plates (0.25 mm). Preparative TLC was performed on E. Merck precoated silica gel plates (1.0, 2.0 mm). Column chromatography was performed by the method of Still *et al.* (20) with E. Merck silica gel 60 (230–400 mesh).

Enedione 8

A solution of 100 g (0.79 mol) of 2-methyl-1,3-cyclohexanedione and 1.5 g (0.03 mol) of potassium hydroxide in 600 mL of anhydrous methanol was brought to reflux and 100 g (1.19 mol) of ethyl vinyl ketone was added dropwise over 1 h. The stirred solution was refluxed for an additional 3 h, and then the methanol was evaporated *in vacuo*. The residue was taken up in 400 mL of benzene and 5 mL (0.06 mol) of pyrrolidine was added. The solution was refluxed for 24 h with azeotropic removal of water. The dark reaction mixture was cooled and 200 mL of ether was added. The solution was washed once with 5% HCl, twice with brine, and then dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure to give a dark oil, which recrystallized from ether to give 76 g of solid. A further 26 g of compound was obtained after column chromatography of the mother liquor to give 102 g (67%) in total of enedione **8** (mp 46–48°C). IR ($CHCl_3$): 2950 (m), 2900 (m), 1720 (s), 1670 (s), 1610 (m), 1365 (m), 1340 (m), 1320 (m); NMR (200 MHz, $CDCl_3$): 3.0–2.0 (m, 9H), 1.83 (s, 3H), 1.83–1.7 (m, 1H), 1.43 (s, 3H); HRMS (EI) *m/e* (relative intensity): 192.1151 (M^+, 100).

Ethynylcarbinol 9

To a −78°C solution of 7.2 g (1.04 mol) of lithium metal in 2.5 L of ammonia, acetylene gas was bubbled in until the dark blue solution became colorless. To this was then added 100 g (0.51 mol) of **8** in 500 mL of anhydrous ether dropwise over 0.5 h. The reaction mixture was stirred for 1 h at −78°C and then carefully quenched with 600 mL of saturated ammonium chloride. After evaporation of the ammonia the aqueous phase was extracted with four 200-mL portions of chloroform. The combined organic phases were washed with water, brine, and then dried over anhydrous magnesium sulfate and filtered. Concentration of the filtrate gave a brown solid, which was recrystallized from ethanol to give 99.0 g (87%) of **9** (mp 135–138°C). IR ($CHCl_3$): 3610 (w), 3310 (m), 2950 (m), 1650 (s), 1610 (m), 1340 (m), 1310 (m); UV (95% ethanol): 251 nm (ϵ = 25 450); NMR (200 MHz, $CDCl_3$): 2.80–1.80 (m, 11H), 1.80 (s, 3H), 1.30 (s, 3H); HRMS (EI) *m/e* (relative intensity): 218.1308 (M^+, 100).

Dienol diacetate 10

A solution of 40.19 g (0.18 mol) of carbinol **9**, 3.0 g (0.016 mol) of *p*-toluenesulfonic acid, and 250 mL of acetic anhydride was stirred for 18 h. The reaction mixture was poured carefully into 500 mL of ice water, stirred for 1 h, and then filtered. The aqueous phase was extracted once with chloroform and combined with the solid obtained from the filtration. The combined organics were dried with anhydrous magnesium sulfate, filtered, and solvent evaporated under reduced pressure. The solid obtained was recrystallized from ethanol to give 51.0 g (92%) of diacetate **10** (mp 120–122°C). IR ($CHCl_3$): 3325 (s), 2950 (m), 1750 (s), 1740 (s), 1675 (m), 1370 (s), 1150 (s), 1095 (s); UV (95% ethanol): 235 nm (ϵ = 22 500); NMR (200 MHz, $CDCl_3$): 5.62 (t, J = 4 Hz, 1H), 2.93–2.78 (m, 1H), 2.54 (s, 1H), 2.18 (s, 3H), 2.06 (s, 3H), 1.65 (t, J = 1.5 Hz, 3H), 1.18 (s, 3H); HRMS (EI) *m/e* (relative intensity): 302.1523 (41).

Diene dione 11

A solution of 5 g (0.017 mol) of **10** in 20 mL of 88% formic acid was refluxed for 2 h. The formic acid was then removed under reduced pressure. The residue was taken up in 50 mL of ethyl acetate and washed with 5% $NaHCO_3$, water, and brine, dried with anhydrous $MgSO_4$, filtered, and solvent evaporated under reduced pressure. The solid was recrystallized from ether to give 2.45 g (68%) of diene dione **11** (mp 104–107°C). IR ($CHCl_3$): 2950 (w), 1660 (s), 1630 (m), 1370 (m); UV (95% ethanol): 240 nm (ϵ = 24 200); NMR (200 MHz, $CDCl_3$): 7.06–6.96 (m, 1H), 2.94–2.4 (m, 6H), 2.33 (s, 3H), 2.30–2.16 (m, 2H), 1.83 (s, 3H), 1.58 (s, 3H); HRMS (EI) *m/e* (relative intensity): 218.1308 (100).

Dithiane 12

A solution of 5 g (22.9 mmol) of **11** in 30 mL of anhydrous ether was cooled in an ice bath and 5 mL (40.7 mmol) of boron trifluoride etherate was added, followed by 3.5 mL (34.4 mmol) of 1,3-propane dithiol. The reaction mixture was stirred for 18 h and then poured carefully into 100 mL of 10% $NaHCO_3$. After separation of the layers the organic phase was washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and evaporated *in vacuo*. The solid was recrystallized from ether to deliver 5.81 g (82%) of dithiane **12** (mp 148–150°C). IR ($CHCl_3$): 2920 (m), 1670 (s), 1360 (m); UV (95% ethanol): 230 nm (ϵ = 16 100), 209 nm (ϵ = 22 800); NMR (200 MHz, $CDCl_3$): 6.90–5.98 (m, 1H), 3.24–2.98 (m, 2H), 2.80–2.50 (m, 3H), 2.28 (s, 3H), 2.01 (s, 3H), 1.45 (s, 3H); HRMS (EI) *m/e* (relative intensity): 308.1270 (100).

Nitriles 3 and 13

A solution of 10 g (0.03 mol) of **12** in 100 mL of DMF was stirred until a uniform solution was obtained. Then a solution of 4.23 g (0.065 mol) of potassium cyanide and 2.68 g (0.05 mol) of ammonium chloride in 30 mL of water was added and the reaction mixture was heated at 80°C for 16 h. Upon cooling, 500 mL of water was added and the solution was thoroughly extracted with ethyl acetate (5 × 150 mL). The combined organic phases were washed with water, brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. Silica gel chromatography (4:1 hexane/ethyl acetate as eluant) gave 7.07 g of **3** and 1.28 g of **13** (77% combined yield). An analytical sample of each was obtained by recrystallization from ethyl acetate: **3** (mp 163–167°C, 192–197°C); IR ($CHCl_3$): 2950 (s), 2240 (m), 1720 (s), 1360 (s); NMR (200 MHz, $CDCl_3$): 3.18–2.96 (m, 3H), 2.78–2.50 (m, 5H), 2.29 (s, 3H), 1.98 (s, 3H), 1.96–1.56 (m, 4H), 1.48 (s, 3H); Anal. calcd. for $C_8H_{25}OS_2N$: C 64.43, H 7.51, N 4.17; found: C 64.50, H 7.52, N 4.19. **13** (mp 182–183°C); IR ($CHCl_3$): 2920 (m), 2240 (w), 1710 (s), 1350 (s); NMR (200 MHz, $CDCl_3$): 3.20–2.98 (m, 3H), 2.82–2.52 (m, 5H), 2.36 (s, 3H), 1.98 (s, 3H), 1.10 (s, 3H). Anal. calcd. for $C_8H_{25}OS_2N$: C 64.43, H 7.51, N 4.17; found: C 64.31, H 7.62, N 4.24.

Enone 14

A solution of 7.0 g (0.021 mol) of **3** in 100 mL of acetonitrile was treated with 6.98 g (0.052 mol) of *N*-chlorosuccinimide and 8.87 g (0.052 mol) of silver nitrate in 40 mL of 80% aqueous acetonitrile. The reaction mixture was stirred at room temperature for 2 h after which it was washed with saturated Na_2SO_3, saturated $NaHCO_3$, and brine. The organic solution was then dried over anhydrous $CaCl_2$ and filtered through Celite. The cake was thoroughly washed with methylene chloride/hexane (1:1), and the combined organic phases were evaporated under reduced pressure. Crystallization of the solid gave 4.1 g (80%) of **14** (mp 130–132°C). IR ($CHCl_3$): 2925 (m), 2240 (w), 1715 (s), 1660 (s), 1610 (m), 1360 (m); UV (95% ethanol): 246 nm (ϵ = 18 509); NMR (60 MHz, $CDCl_3$): 3.38–2.40 (m, 8H), 2.30 (s, 3H), 1.82 (s, 3H), 1.67 (s, 3H); MS (EI) *m/e* (relative intensity): 245 (M^+, 100).

Dienol acetate 15

A solution of 3.5 g (14.28 mmol) of **14** in 20 mL of acetic anhydride was treated with 0.5 mL of acetic anhydride/48% aqueous hydrobromic acid (3:2) and stirred for 16 h. The reaction mixture was then poured carefully into 100 mL of ice water and stirred for 1.5 h. The solidified product was taken up in chloroform and the aqueous phase was thoroughly extracted with chloroform (4 × 50 mL). The combined

organic phases were carefully washed with saturated $NaHCO_3$, water, and brine, and dried over anhydrous $CaCl_2$. Filtration and evaporation of solvent gave a brown solid, which was purified on silica gel chromatography (hexane/ethyl acetate 3:2 as eluant) to give 3.6 g (88%) of product. An analytical sample of **15** (125–127°C) was obtained by recrystallization from ethanol. IR ($CHCl_3$): 2910 (m), 2240 (w), 1740 (s), 1700 (s), 1665 (m), 1365 (s), 1350 (s); NMR (200 MHz, $CDCl_3$): 5.65 (t, J = 4 Hz, 1H), 3.22–3.1 (m, 1H), 2.77–2.42 (m, 4H), 2.36 (s, 3H), 2.20 (s, 3H), 1.68 (t, J = 2 Hz, 3H), 1.40 (s, 3H); MS (EI) m/e (relative intensity): 287 (M^+, 100).

Bromo dienol acetate ***16***

A solution of 200 mg (0.69 mmol) of **15** in 10 mL of anhydrous THF was treated with 260 mg (0.69 mmol) of phenyl trimethyl ammonium tribromide. The reaction mixture was stirred for 0.75 h and then poured into saturated $NaHCO_3$. The layers were separated and the aqueous phase was washed with two 5-mL portions of ether. The combined organic phase was washed several times with aqueous Na_2SO_3 until the aqueous phase was clear. Drying over anhydrous $CaCl_2$, filtering, and evaporation of solvent under reduced pressure gave 280 mg of a mixture of unstable bromide **16** and acetate **15**. This compound was always generated *in situ* for use in the next synthetic transformation. IR ($CHCl_3$): 2920 (m), 2240 (w), 1745 (s), 1720 (s), 1660 (m), 1370 (m), 1360 (m); NMR (60 MHz, $CDCl_3$): 5.75–5.52 (m, 1H), 4.0 (s, 2H), 2.20 (s, 3H), 1.68 (s, 3H), 1.45 (s, 3H); MS (EI) m/e: 367/365 (M^+).

Diester ***17***

A solution of **16**, prepared as described above, was treated directly with the sodium anion of dimethyl-1,3-acetone dicarboxylate, generated by stirring a solution of 50.1 mg (2.09 mmol) of sodium hydride with 0.31 mL (2.09 mmol) of dimethyl-1,3-acetone dicarboxylate for 1 h, followed by addition of 0.1 mL of HMPA. The reaction mixture was allowed to stir overnight and then poured into saturated aqueous NH_4Cl. The aqueous phase was extracted with ethyl acetate and the combined organic washings were dried over anhydrous $CaCl_2$, filtered, and solvent evaporated. Purification on 1 mm silica gel preparative TLC plates (hexane/ethyl acetate 1:1 as eluant) furnished 80 mg starting dienol acetate **15** and 100 mg (52%) of diester **17**. IR ($CHCl_3$): 2920 (m), 2240 (w), 1740 (s), 1730 (s), 1710 (s), 1660 (m), 1430 (m), 1360 (m), 1350 (m); UV (95% ethanol) 234 nm (ϵ = 15 643), (95% ethanol + 5% NaOH): 240 nm (ϵ = 14 107) (hydrolysis of enol acetate to enone), 280 nm (ϵ = 12 286) (enolate of β-keto ester); NMR (200 MHz, $CDCl_3$): 5.64 (t, J = 4 Hz, 1H), 4.72 and 4.74 (s, 1H), 4.38–4.32 (m, 1H), 3.78 (s, 6H), 3.26–3.06 (m, 3H), 2.18 (s, 3H), 1.68 (s, 3H), 1.36, 1.38, and 1.42 (s, 3H); MS (EI) m/s: 459 (M^+).

Malonyl dienol acetate ***18***

To a solution of **16** in 15 mL of THF was added the sodium anion of dimethyl malonate, prepared from 101 mg (4.2 mmol) of NaH and 0.48 mL (4.2 mmol) of dimethyl malonate in 15 mL of THF. The reaction mixture was stirred for 2 h and then quenched with 10 mL of saturated aqueous NH_4Cl. The layers were separated and the aqueous phase was washed with three 10-mL portions of ether. The combined extracts were dried over anhydrous $CaCl_2$, filtered, and evaporated under reduced pressure. The residue was purified on 1 mm silica gel preparative TLC plates (two developments with hexane/ethyl acetate 3:2 as eluant) to give 100 mg of dienol acetate **15** and 99 mg (68%) of malonyl adduct **18**. IR ($CHCl_3$): 2910 (w), 2240 (w), 1730 (s), 1740 (s), 1430 (m), 1415 (m), 1350 (m); NMR (200 MHz, $CDCl_3$): 5.57 (t, J = 4 Hz, 1H), 4.01 (t, J = 8 Hz, 1H), 3.73 (s, 6H), 3.2–3.06 (m, 3H), 2.8–2.28 (m, 6H), 2.20 (s, 3H), 1.67 (t, J = 2 Hz, 3H), 1.40 (s, 3H); MS (EI) m/e: 417 (M^+).

Tetraester ***19***

To a solution of 60 mg (0.14 mmol) of **18** in 10 mL of THF was added 10 mg (0.42 mmol) of sodium hydride. The reaction mixture was stirred for 1.5 h and then 30 mg (0.17 mmol) of dimethyl chloromethylene malonate was added and stirring continued for 0.5 h. The reaction mixture was diluted with 10 mL of ether and then poured carefully into water. The layers were separated and the organic phase was dried with anhydrous $CaCl_2$, filtered, and evaporated under reduced pressure. The residue was purified on 1 mm silica gel preparative TLC plates (hexane/ethyl acetate 3:2 as eluant) to deliver 56 mg (72%) of tetraester **19**. IR ($CHCl_3$): 2940 (m), 2840 (w), 2240 (w), 1730 (s), 1430 (m), 1365 (m); UV (95% ethanol): 231 nm (ϵ = 16 765), 235 nm (ϵ = 16 646), (95% ethanol, 5% NaOH), 400 nm (ϵ = 11 353), 390 nm (ϵ = 10 176); NMR (200 MHz, $CDCl_3$): 7.79 (s, 1H), 5.64 (t, J = 4 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.22–3.10 (m, 2H), 2.80–2.26 (m, 4H), 2.16 (s, 3H), 1.67 (s, 3H), 1.34 (s, 3H); MS (EI) m/e: 459 (M^+).

Phenyl selenide ***21***

A solution of 100 mg (0.24 mmol) of **18** in 15 mL of benzene was treated with 50.5 mg (2.5 mmol) of phenyl selenyl chloride followed by 58.3 mg (2.5 mmol) of silver trifluoroacetate. The reaction mixture was stirred at room temperature for 6 h and then filtered through Celite. The cake was washed thoroughly with chloroform and the combined organic phases were evaporated under reduced pressure. Purification on silica gel preparative TLC plates (hexane/ethyl acetate 3:2 as eluant) gave 95 mg (75%) of selenide **21**. IR ($CHCl_3$): 2940 (w), 2240 (w), 1750 (s), 1730 (s), 1660 (s), 1600 (w), 1430 (m), 1355 (m); NMR (200 MHz, $CDCl_3$): 7.83–7.70 (m, 2H), 7.58–7.45 (m, 3H), 4.48 (t, J = 2 Hz, 1H), 4.08 (t, J = 8 Hz, 1H), 3.86 (s, 6H), 3.72 (dd, J = 12 Hz, J = 20 Hz, 2H), 3.27 (dd, J = 12 Hz, J = 6 Hz, 2H), 2.86–2.13 (m, 6H), 2.02 (s, 3H), 1.65 (s, 3H).

Tetraester phenyl selenide ***22***

A solution of 40 mg (0.08 mmol) of **21** and 10 mL of THF was treated with 3.6 mg (0.15 mmol) of sodium hydride for 1.5 h. To this was added 30 mg (0.17 mmol) of dimethyl chloromethylene malonate and the reaction mixture was stirred for an additional hour. The solution was filtered through a glass wool plug and diluted with 10 mL of ethyl acetate. After washing with water and brine, the organic phase was dried over anhydrous $CaCl_2$, filtered, and the solvent evaporated. The yellow oil obtained was purified on silica gel preparative TLC plates (hexane/ethyl acetate 3:2 as eluant) to deliver 25 mg (47%) of phenyl selenide tetramethylester **22**. IR ($CHCl_3$): 2940 (m), 2920 (m), 2240 (w), 1740 (s), 1665 (m), 1430 (m), 1355 (m); NMR (200 MHz, $CDCl_3$): 7.85 (s, 1H), 7.80–7.64 (m, 2H), 7.51–7.38 (m, 3H), 4.38 (t, J = 2 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 6H), 3.78 (s, 3H), 2.74–2.29 (m, 6H), 1.94 (s, 3H), 1.52 (s, 3H).

Tertiary alcohol ***23***

A solution of 30 mg (0.045 mmol) of selenide **22** in 10 mL of THF was treated with 17.7 mg (0.09 mmol) of 85% mCPBA and stirred for 2 h. The reaction mixture was washed with saturated Na_2SO_3, $NaHCO_3$, water, and brine. After drying over anhydrous $CaCl_2$ and filtering, the solvent was evaporated under reduced pressure. Purification on silica gel preparative TLC plates (hexane/ethyl acetate 3:2) gave 19 mg (80%) of alcohol **23**. IR ($CHCl_3$): 2940 (m), 2920 (m), 2840 (m), 2240 (w), 1740 (s), 1720 (s), 1430 (m), 1360 (m); NMR (200 MHz, $CDCl_3$): 7.78 (s, 1H), 6.22 (t, J = 2 Hz, 1H), 3.83 (s, 3H), 3.80 (s, 9H), 3.22–3.13 (m, 1H), 3.0–2.86 (m, 1H), 2.74–1.99 (m, 7H), 1.66 (s, 3H), 1.58 (s, 3H).

General procedure for Michael reactions with the dianion: Generation of ***34***

A solution of LDA in 5 mL of dry THF (0.64 mmol, 3.2 equiv.) was cooled to −78°C and 100 mg (0.2 mmol) of **3** in 5 mL of dry THF was added via syringe over 2 min. The reaction was stirred at this temperature for 2 h at which time 60 mg (0.38 mmol) of dimethyl ethylidene malonate **25** in 0.5 mL of THF was added in one lot. After stirring for an additional 15 min at −78°C, the reaction mixture was poured into saturated NH_4Cl. The layers were separated and the aqueous phase was extracted with ethyl acetate. The combined extracts were washed with water and brine, dried over anhydrous $CaCl_2$, and filtered. The solvent was evaporated *in vacuo* and the resultant oil was chromatographed on silica gel preparative plates (hexane/ethyl acetate 3:2 as eluant) to deliver 70 mg (49%) of Michael adduct **34** as a 1:2 mixture of C14 diastereoisomers. IR ($CHCl_3$): 2960 (s), 2240 (w), 1750 (s), 1730 (s), 1440 (s), 1380 (m), 1360 (m); NMR (200 MHz, $CDCl_3$), major diastereomer: 3.78 (s, 6H), 3.19–2.96 (m, 3H), 2.83–2.48 (m, 6H), 2.36 (s, 3H), 2.0 (s, 3H), 1.44 (s, 3H), 1.32 (d, J = 8 Hz, 3H); minor diastereomer: 3.80 (s, 6H), 3.19–2.96 (m, 3H), 2.83–2.48 (m, 6H),

2.37 (s, 3H), 2.0 (s, 3H), 1.44 (s, 3H), 1.12 (d, J = 8 Hz, 3H); MS (EI) m/e: 493 (M^+).

Enyne alcohol ***40***

A suspension of 4.29 g (0.18 mol) of magnesium metal in 150 mL of dry ether was treated with 21.5 g (0.18 mol) of allyl bromide in 50 mL of ether. When the metal had been completely consumed, 8.87 g (0.07 mol) of aldehyde **39** in 30 mL of ether was added dropwise from a dropping funnel over 15 min. The reaction mixture was stirred for 2 h and then poured into cold 5% HCl. The layers were separated and the organic phase was washed with water and brine. After drying over anhydrous $MgSO_4$ and filtration, the solvent was evaporated under reduced pressure. Pure alcohol **40** (bp 48–50°C, 10 Torr (1 Torr = 133.3 Pa)) was obtained by vacuum distillation, 8.24 g (62%). IR ($CHCl_3$): 3600 (m), 2960 (m), 2180 (m), 1650 (m), 1390 (m), 1260 (m), 1030 (s); NMR (200 MHz, $CDCl_3$): 6.02–5.76 (m, 1H), 5.50–5.36 (m, 2H), 4.44 (t, J = 6 Hz, 1H), 2.49 (dd, J = 6 Hz, J = 7 Hz, 2H), 0.17 (s, 9H).

Mesylate ***41***

A solution of 4.35 g (0.026 mol) of alcohol **40** in 10 mL of dry DMF was cooled in an ice bath and treated with 4.04 g (0.031 mol) of 2,4,6-collidine and 3.52 g (0.031 mol) of methane sulfonyl chloride. The reaction mixture was allowed to warm to room temperature and stir for 3 h. It was then poured into ice water and diluted with 100 mL of hexane. The layers were separated and the organic phase was washed with saturated $NaHCO_3$, water, and brine. After drying over anhydrous $MgSO_4$ and filtration, the solvent was evaporated under reduced pressure. The crude mesylate **41** obtained, 6.2 g (96%), was used without further purification. IR ($CHCl_3$): 2940 (w), 2170 (w), 1640 (w), 1415 (w), 1360 (s), 1330 (m), 1180 (s); NMR (200 MHz, $CDCl_3$): 5.96–5.72 (m, 1H), 5.30–5.08 (m, 3H), 3.11 (s, 3H), 2.62 (dd, J = 6 Hz, J = 6 Hz, 2H), 0.18 (s, 9H).

General procedure for halide formation: Preparation of iodide ***44***

A solution of 6.2 g (0.025 mol) of mesylate in 100 mL of anhydrous acetone and 9 g (0.059 mol) of KI was refluxed for 12 h. Upon cooling and evaporation of solvent under reduced pressure the residue was taken up in 200 mL of hexane and 100 mL of water. The layers were separated and the organic phase was successively washed with water, $Na_2S_2O_3$, and brine, dried over anhydrous $MgSO_4$, filtered, and solvent evaporated under reduced pressure. The oil was distilled under vacuum (0.01 Torr) to yield 4.25 g (61%) of iodide **44** (bp 53–56°C). IR ($CHCl_3$): 2960 (s), 2920 (s), 2180 (s), 1680 (m), 1650 (s), 1630 (m), 1420 (s); NMR (200 MHz, $CDCl_3$): 5.96–5.73 (m, 1H), 5.29–5.10 (m, 2H), 4.53 (t, J = 7 Hz, 1H), 2.72 (dd, J = 7 Hz, J = 7 Hz, 2H), 0.16 (s, 9H).

Alkylated adduct ***47***

A solution of 0.057 mL (0.69 mmol) of pyrrolidine in 10 mL of dry THF was cooled to −78°C and 0.43 mL (0.69 mmol) of 1.5 M *n*BuLi in hexane was added via a syringe. After stirring for 15 min, 100 mg (0.3 mmol) of nitriles **3** and **13** in 1 mL of THF was added and stirring was continued for 2 h. Then 0.066 mL (0.3 mmol) of iodide **44** was added neat in one lot. Following stirring at −78°C for 1 h the reaction mixture was poured into saturated NH_4Cl. The layers were separated and the organic portion was washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. After evaporation of solvent under reduced pressure, the oil was purified by silica gel chromatography (hexane/ethyl acetate 9:1 → 3:1 as eluant) to give 61 mg (95%) of alkylation product **47** and 56 mg of nitriles **3** and **13**. IR ($CHCl_3$): 2950 (s), 2880 (m), 2250 (w), 2180 (m), 1710 (s), 1650 (m), 1420 (m), 1360 (m); NMR (200 MHz, $CDCl_3$): 5.98–5.72 (m, 1H), 5.23–5.06 (m, 3H), 3.17 (s, 1H), 3.16–2.96 (m, 3H), 2.80–2.46 (m, 8H), 2.38 (s, 3H), 2.05 (s, 3H), 2.04–1.42 (m, 4H), 1.41 (s, 3H), 0.18 (s, 9H); MS (EI) m/e: 485 (M^+).

Acknowledgements

Support by the Natural Sciences and Engineering Research Council of Canada, Ottawa, in the form of operating grants and a fellowship to one of us (D.I.M.) is gratefully acknowledged. We thank Dr. Peter S. White of this department for the X-ray crystallographic determinations and Dr. Zarko Stojanac of this department for suggesting the strategic concept involving the formation of bonds 1 and 2 in Fig. 1.

1. J. POLONSKY. Fortschr. Chem. Org. Naturst. **30**, 101 (1973).
2. J. POLONSKY. Fortschr. Chem. Org. Naturst. **47**, 222 (1985).
3. (*a*) S. M. KUPCHAN, J. A. LACADIE, G. N. HOWIE, and B. R. SICKLES. J. Med. Chem. **19**, 1130 (1976); (*b*) M. E. WALL and W. C. WANI. J. Med. Chem. **21**, 1186 (1978).
4. (*a*) M. KIM, K. KAWADA, R. S. GROSS, and D. S. WATT. J. Org. Chem. **55**, 504 (1990); (*b*) P. A. GRIECO, R. P. NARGUND, and D. T. PARKER. J. Am. Chem. Soc. **111**, 6287 (1989); (*c*) T. K. M. SING, Y. TANG, and J. F. MALONE. J. Chem. Soc. Chem. Commun. 1294 (1989); (*d*) P. A. GRIECO, D. T. PARKER, P. GARNER, and S. SASAKI. Tetrahedron Lett. **30**, 3401 (1989); (*d*) M. KIM, K. KAWADA, and D. S. WATT. Synth. Commun. **19**, 2017 (1989); (*f*) K. KAWADA, M. KIM, and D. S. WATT. Org. Prep. Proced. Int. **21**, 521 (1989); (*g*) S. DARVESH, A. S. GRANT, D. I. MAGEE, and Z. VALENTA. Can. J. Chem. **67**, 2237 (1989), and references therein; (*h*) M. SASAKI, T. MURAE, and T. TAKAHASHI. J. Org. Chem. **55**, 528 (1990).
5. (*a*) P. A. GRIECO, S. FERRINO, and G. J. VIDARI. J. Am. Chem. Soc. **106**, 3539 (1984); (*b*) P. A. GRIECO, R. LIS, S. FERRINO, and J. Y. YAW. J. Org. Chem. **49**, 2342 (1984); (*c*) P. A. GRIECO, D. PARKER, and R. P. NARGUND. J. Am. Chem. Soc. **110**, 5568 (1988); (*d*) H. HIROTA, A. YOKOYAMA, K. MIYAJI, T. NAKAMURA, and T. TAKAHASHI. Tetrahedron Lett. **28**, 435 (1987).
6. A. B. MEKLER, S. RAMACHANDRAN, S. SWAMINATHAN, and M. S. NEWMAN. Org. Synth. **41**, 56 (1961).
7. (*a*) M. S. NEWMAN, S. RAMACHANDRAN, S. K. SANKARAPPA, and S. SWAMINATHAN. J. Org. Chem. **26**, 727 (1961); (*b*) H. RUPE and E. KAMBLI. Helv. Chim. Acta, **9**, 672 (1926).
8. (*a*) R. A. DANIEWSKI, P. S. WHITE, and Z. VALENTA. Can. J. Chem. **57**, 1397 (1979); (*b*) R. A. DANIEWSKI, Z. VALENTA, and P. S. WHITE. Bull. Pol. Acad. Sci. **32**, 29 (1984).
9. E. J. COREY and B. W. ERICKSON. J. Org. Chem. **36**, 3553 (1971).
10. A. MARQUET and J. JACQUES. Tetrahedron Lett. No. 9, 24 (1959).
11. H. J. REICH, J. M. RENGA, and I. L. REICH. J. Am. Chem. Soc. **97**, 5334 (1975).
12. D. L. J. CLIVE. Tetrahedron, **34**, 1039 (1978).
13. M. ZÜGER, T. WELLER, and D. SEEBACH. Helv. Chim. Acta, **63**, 2005 (1980).
14. D. SEEBACH and J. GOLINSKI. Helv. Chim. Acta, **64**, 1413 (1981).
15. (*a*) R. B. MILLER. Synth. Commun. **2**, 267 (1972); (*b*) T. R. BORONOEVA, N. N. BELYAEV, M. D. STADNICHUK, and A. A. PETROV. Zh. Obshch. Khim. **44**, 1949 (1973).
16. G. HELMCHEN, A. SELIM, D. DORSCH, and I. TAUFER. Tetrahedron Lett. **24**, 3213 (1983).
17. S. HANESSIAN, A. UGONLINI, D. DUBE, P. J. HODGES, and C. ANDRE. J. Am. Chem. Soc. **108**, 2776 (1986).
18. U. EDER, G. SAUER, and R. WIECHERT. Angew. Chem. Int. Ed. Engl. **10**, 496 (1971); Z. G. HAJOS and D. R. PARRISH. J. Org. Chem. **39**, 1615 (1974; J. GUTZWILLER, P. BUCHSCHACHER, and A. FURST. Synthesis, 167 (1977).
19. D. D. PERRIN and W. L. F. ARMAREGO. Purification of laboratory chemicals. 2nd ed. Pergamon Press, Toronto. 1980.
20. W. C. STILL, M. KAHN, and A. MITRA. J. Org. Chem. **43**, 2933 (1978).