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THE SYNTHESIS OF AMINO ACIDS BY 1,3-DIPOLAR CYCLOADDITIONS OF AZOMETHINE YLIDES

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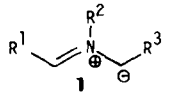
Abstract—Thiazolium ylides react with a variety of dipolarophiles to afford adducts. After filtration chromatography, a tricyclic adduct is obtained. The tricyclic adducts react with potassium t-butoxide/t-butanol to provide dihydropyrroles. The adducts also react with tributyltin hydride to form compounds in which the thiazolidine ring has been cleaved. These adducts can be hydrolyzed under acidic conditions to form pyrrolidines. The desulfurization procedure is significant in that none of the relative asymmetry derived from the dipolar cycloaddition is lost. The synthesis of α-allokainic acid has been achieved from adduct **16s**.

In recent years the application of 1,3-dipolar cycloadditions[1-5] to the synthesis of natural products has increased dramatically.[6,7] One subset of ylides, the azomethine ylides (**1**), has now become very useful



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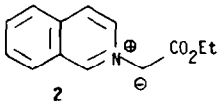
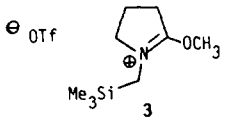
synthetically as a result of variations in the appendages R^1, R^2 and R^3. For example, incorporation of R^1 and R^2 as part of an aromatic ring[8] as in **2**. Many ylides



2

derived from the reaction of a heterocyclic compound with an α-halocarbonyl compound are known.[9-15] Several groups have developed precursors to ylide **1** wherein the stabilizing groups R^1, R^2 and R^3 can be removed after the cycloaddition. These include iminoether **3**,[16] silane **4**[17] and the thiazolium salt **5**.[18] Recently, Padwa and Chen have developed a precursor to the parent azomethine ylide **6** from the cyanosilane **7**.[19]



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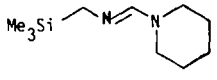

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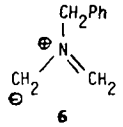

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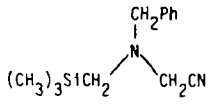

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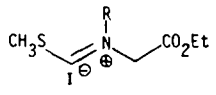
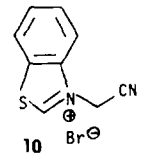
We initiated our research effort by examining the sulfur stabilized iminium salts **8–10**. The ylides generated by the reaction of **8** or **9** with base did not



8, R=CH_3
9, R=Ph



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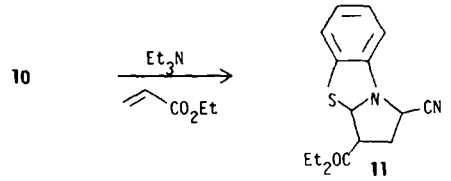
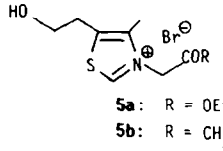
afford 1,3-dipolar cycloaddition products with either ethyl acrylate or dimethyl maleate. The ylide generated from **10** did produce adduct **11** in modest yield. However, the ylide from **10** failed to react with other



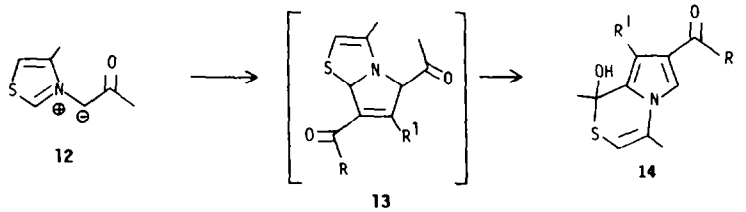
11

dipolarophiles. We then examined ylides derived from **5**. We were aware that Potts *et al.*[20] had examined the reaction of ylide **12** with several acetylenic dipolarophiles and had observed that the initial adducts **13** rearranged to form pyrroles as the only isolable



5a: R = OEt
5b: R = CH_3

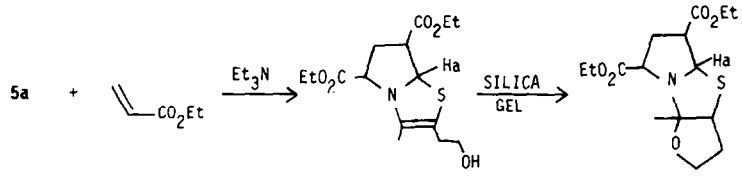
products. Generating the ylide of salt **5a** (available[20] by reacting the thiazole with ethylbromoacetate in alcohol) with triethylamine and reacting it with 1 equiv of ethyl acrylate produced the bicyclic molecule assigned structure **15a**. The ^{1}H-NMR spectrum seemed to confirm this assignment. It contained two unique ethyl ester groups, a sharp downfield doublet at δ 5.20



12 → **13** → **14**

(tentatively ascribed to H_a) and a sharp methyl singlet appearing at δ 1.50. A mass spectrum also supported this structure. Along with the adduct, a small amount of colored, very polar material was formed during the course of the reaction. Passage of the crude mixture over a short silica gel column easily separated the two components; however, the isolate had a slightly different ^{1}H-NMR spectrum. The downfield doublet now appeared at δ 5.60 and the methyl singlet at δ 1.60. The bicyclic molecule **15a** had cyclized to form tricyclic diester **16a** upon exposure to silica gel.

General methods for cleavage of the tricyclic skeletons to yield pyrrolidines with preservation of the stereochemical centers created by the initial dipolar addition were explored. Our initial attempts using strong acids, strong bases, metal hydrogenation catalysts (Raney Ni, Rh/C, Ru/C), $NiCl_2 \cdot 6H_2O/NaBH_4$, $CuBr_2/NaCNBH_3$, $BF_3 \cdot OEt_2/Et_3SiH$, CuI/Et_3SiH, MCPBA, Al–Hg, and dissolving metal reductions (Li, Na, Ca in NH_3) were unsuccessful. Either starting material or products arising from attack at other sites in the molecule were recovered.



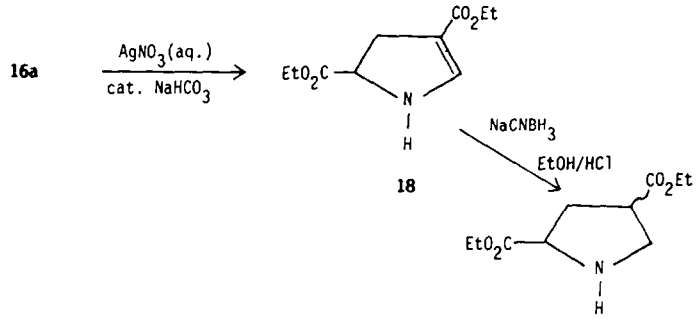
15a **16a**

This structural assignment appeared to fit all of the data, especially the disappearance of both the olefinic absorbance (1550, 1540 cm^{-1}) and the hydroxyl absorbance (3510 cm^{-1}) in the IR spectrum. A single crystal X-ray structure of adduct **16s** concretely confirmed this structural assignment. In some cases a mixture of diastereomers was formed at the newly formed quaternary center. This is evidenced by two sets of doublets (H_a) appearing downfield between δ 5 and 6. Equilibration to one isomer is possible with CF_3CO_2H.

The results of a study of the cycloadditions of thiazolium salts with a variety of mono-, di-, tri- and tetrasubstituted olefins are compiled in Table 1. The yields of cycloadducts were found to be significantly higher when a *heterogeneous* solution of thiazolium salt in acetonitrile was reacted, compared to when a homogeneous stirred solution in dimethylformamide was used. The initial adducts were all converted into tricyclic compounds by exposure to silica gel because the tricyclic compounds tended to be significantly more stable.

The initial determination of the regiochemistry of the cycloaddition reaction was made by comparing the diethyl 2,4-pyrrole dicarboxylate **17** (prepared from adduct **16a**) with a sample of authentic material synthesized via permanganate oxidation of ethyl 4-formyl-2-pyrrole carboxylate prepared by the route of Sonnet.[21] Product **17** was identical to authentic diethyl 2,4-pyrrole dicarboxylate by ^{1}H-NMR and by TLC.

We next proceeded to investigate other bond cleavage conditions. A method reported by Luhowy *et al.*[22] for the hydrolysis of thiazolidines proved to be moderately successful. Under aqueous conditions in the presence of silver(I), **16a** was cleaved in 67% yield to 3,5-dicarbethoxy-Δ^2-pyrroline (**18**), which compared closely to the similar diester prepared by Saegusa *et al.*[23] The enamine **18** was then reduced with sodium cyanoborohydride to diethyl 2,4-pyrrolidine dicarboxylate (**19**), as a mixture of diastereomers, in 86% yield via the method of Borch *et al.*[24]

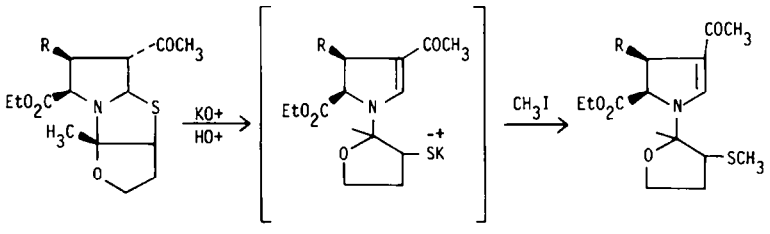


18 **19**

The silver(I) cleavage has been tested on a number of tricyclic systems with excellent results, although the stereochemistry at C-4 is lost. Compounds **16b**, **16h**, **16n**, **16g**, **16s** and **16t** yielded Δ^1- or Δ^2-pyrrolines in high yields.

In the system where an acidic proton is available on the C-4 carbon atom, strong equilibrating bases such as potassium t-butoxide in t-butanol smoothly generated the enolate which opened to the Δ^2-pyrroline. An excess of methyl iodide rapidly methylated the resulting thiolate, similar to the work of Brain *et al.*[25] Cleavage of the α-amino ether with 2 N HCl in EtOH afforded the same Δ^2-pyrroline synthesized earlier via the silver ion route. This two-step procedure proved to be more reproducible and easier to carry out on larger scales.

The Δ^2-pyrrolines containing ketone groups afforded some overreduction products with $NaCNBH_3$. In only a few cases were the reductions reasonably clean. Most



16b R = CH_3

16s R = $(CH_2)_2OBz$

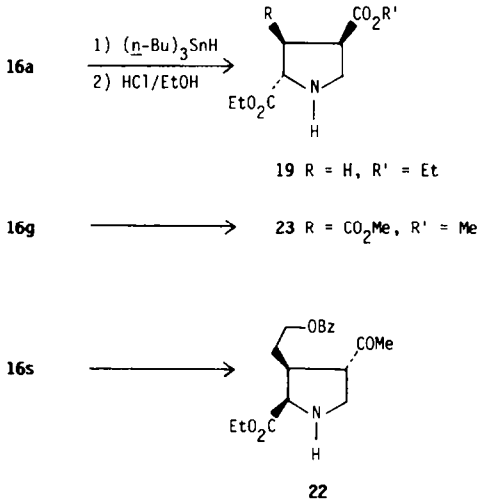
20 R = CH_3

21 R = $(CH_2)_2OBz$

of the reactions were contaminated by side products, and the yields of pyrrolidines were low. Conditions for efficient hydrogenation to the corresponding pyrrolidine were then sought. Catalytic hydrogenations (Pd/C, Raney Ni, Rh/Al) proved unsuccessful, yielding either starting material, pyrroles, or unidentifiable resinous matter. Hydride reductions suffered the same fate as observed with $NaCNBH_3$ reduction—some overreduction to secondary alcohols.

A literature reference[26] prompted us to explore radical cleavages on the initial tricyclic molecules **16**. We were quite delighted to find that in the presence of 1 equiv[27] of tri-n-butyltin hydride and a catalytic amount of AIBN in benzene, **16s** was smoothly cleaved to **22** after treatment with acidic ethanol. The N-t-butoxycarbonyl derivative **22a** was identical (^{1}H-NMR, ^{13}C-NMR, and R_f values on TLC plates) to the epimerized material prepared by the $NaCNBH_3$ procedure.

This radical cleavage process opens up an extremely rapid route from tricyclic adducts **16** to highly substituted pyrrolidines. Importantly, it preserves the stereochemistry produced at three of the four centers derived from the 1,3-dipolar cycloaddition! The generality of this reaction has been demonstrated with a few representative tricyclic systems **16a** and **16g**, yielding pyrrolidines **19** and **23**, respectively.

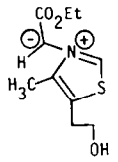


19 R = H, R' = Et

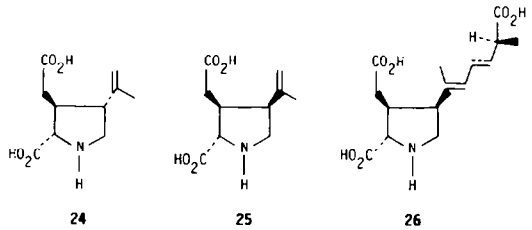
23 R = CO_2Me, R' = Me

22

The structure of **16s** is secure, based on the X-ray determination. The coupling constants in the 300 MHz NMR spectrum of **16b** (the adduct from 3-penten-2-one and **5a**) correspond almost exactly to those in **16s**. Thus, the C-2 ester and the C-4 acetyl group are *trans* in **16b**. The 300 MHz NMR of adduct **16g**, however, displays a quite different pattern. The NOESY (nuclear Overhauser effect) 2D-NMR experiment clearly supports a *trans* relationship between the carboethoxy group at C-2 and the carbomethoxy group at C-3. As a whole, the data are consistent with the reaction of a dipolarophile via an *endo* transition state with the azomethine ylide shown below.



With the successful dipolar addition sequence and two efficient routes to substituted pyrrolidines, we then embarked on the application of this methodology to the synthesis of natural products. Our first target was α-allokainic acid, **24**, an amino acid isolated from the marine algae *Digenea simplex* Ag.[28] Other members of this class include α-kainic acid (**25**) and domoic acid (**26**). Due to the potent neurophysiological activity of **24** in mammals,[29] new routes to **24** continue to be of interest.



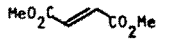
24 **25** **26**

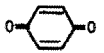
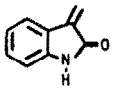
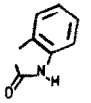
Syntheses by Miyamoto *et al.*[30] and by Honjo[31] were nonstereospecific but served an important function in helping to determine the structure. In an elegant synthesis, Oppolzer and Andres[32] have synthesized **24**, based on an intramolecular ene reaction. They reported the thermal cyclization of their key intermediate to produce pyrrolidine **27** in 97% yield. Compound **24** was subsequently obtained in two steps with high overall yield.

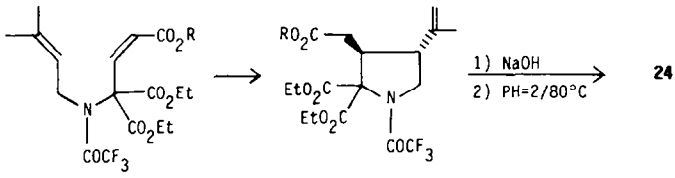
The same workers[33] were able to produce α-kainic acid by a similar intramolecular ene reaction. Recently, Ohfune and Tomita synthesized domoic acid.[34]

Our synthesis employed **22a**, available in four steps from ylide **5**. Removal of the benzyloxy protecting group of N-t-butoxycarbonyl-3α-(2-benzyloxyethyl)-4β-acetyl-α-proline-ethyl-ester with 10% palladium on carbon under a hydrogen atmosphere gave a diastereomeric mixture of hemiketals **28** as evidenced by the loss of the acetyl methyl in the ^{1}H-NMR spectrum. The N-t-butoxycarbonyl group experiences hindered rotation with diastereomeric geometries at

Table 1. The 1,3-dipolar cycloadditions of thiazolium ylides generated *in situ* from thiazolium salts

Entry	Thiazolium salt	Olefin	No. equiv.	Solvent	Temp. (°)	Yield (%)	Adduct	16
1	**5a**	$EtO_2CCH{=}CH_2$	1	DMF	0	55	$R^1 = R^2 = R^4 = H; R^3 = CO_2Et$	**a**
2	**5a**	$EtO_2CCH{=}CH_2$	1	CH_3CN	0	82	$R^1 = R^2 = R^4 = H; R^3 = CO_2Et$	**a**
3	**5a**	$CH_3COCH{=}CHCH_3$	1	DMF	0	Low	$R^1 = R^4 = H; R^2 = CH_3; R^3 = COCH_3$	**b**
4	**5a**	$CH_3COCH{=}CHCH_3$	1	CH_3CN	0	70	$R^1 = R^4 = H; R^2 = CH_3; R^3 = COCH_3$	**b**
5	**5b**	$CH_3COCH{=}CHCH_3$	1	DMF	0	Low	$R^1 = R^4 = H; R^2 = CH_3; R^3 = COCH_3$	**c**
6	**5b**	$CH_3COCH{=}CHCH_3$	1	DMF	45	45	$R^1 = R^4 = H; R^2 = CH_3; R^3 = COCH_3$	**c**
7	**5b**	$CH_3COCH{=}CHCH_3$	1	CH_3CN	23	75	$R^1 = R^4 = H; R^2 = CH_3; R^3 = COCH_3$	**c**
8	**5b**	$CH_3COCH{=}CHCH_3$	1	CH_3CN	0	98	$R^1 = R^4 = H; R^2 = CH_3; R^3 = COCH_3$	**c**
9	**5b**	p-$MePhSO_2CH{=}CH_2$	1	DMF	0	55	$R^1 = R^2 = R^4 = H; R^3 = p$-$MePhSO_2$	**d**
10	**5b**		1	CH_3CN	0	89	$R^1 = R^4 = H; R^2 = R^3 = CO_2Me$	**e**
11	**5b**		1	CH_3CN	0	87	$R^2 = R^4 = H; R^3 = R^1 = CO_2Me$	**f**
12	**5a**		1	CH_3CN	0	50	$R^2 = R^4 = H; R^3 = R^1 = CO_2Me$	**g**
13	**5a**		1	DMF	0	—	—	—
14	**5a**	$CH_3(CH_2)_3CH{=}CH_2$	1	DMF	0	—	—	—
15	**5a**	$CH_3COCH{=}CHPh$	1	CH_3CN	23	77	$R^1 = R^4 = H; R^2 = Ph; R^3 = COCH_3$	**h**
16	**5c**	$EtO_2CCH{=}CH_2$	1	CH_3CN	0	57	$R^1 = R^4 = R^2 = H; R^3 = CO_2Et$	**i**
17	**5c**	$NCCH{=}CH_2$	1	CH_3CN	0	53	$R^1 = R^2 = R^4 = H; R^3 = CN$	**j**
18	**5b**		1	CH_3CN	0	—	—	—

19	5b	$NCCH{=}CH_2$	1	CH_3CN	0	56	$R^1 = R^2 = R^4 = H; R^3 = CN$	k
20	5b	$PhCH{=}CHCHO$	1	CH_3CN	23	—	—	—
21	5b	$CH_3COCH{=}CHPh$	1	CH_3CN	23	52	$R^1 = R^4 = H; R^2 = Ph; R^3 = COCH_3$	l
22	5b	$CH_3CH{=}CHCH{=}CHCO_2Me$	1	CH_3CN	0	—	—	—
23	5c	$CH_3COCH{=}CHCH_3$	1	CH_3CN	23	33	$R^1 = R^4 = H; R^2 = CH_3; R^3 = COCH_3$	m
24	5a		1	DMF	0	- -	—	—
25	5a	$CH_2{=}C(CH_3)CO_2Me$	1	CH_3CN	0	30	$R^1 = R^2 = H; R^4 = CH_3; R^3 = CO_2Me$	n
26	5b	$(CN)_2C{=}C(CN)_2$	1	CH_3CN	0	—	—	—
27	5a		1	CH_3CN	23	55	$R^1 = R^4 = H; R^2, R^3 =$ 	o
28	5a		1	CH_3CN	23	~30	$R^1 = R^2 = H; R^3, R^4 =$ 	p
29	5b		1	CH_3CN	23	~30	$R^1 = R^2 = H; R^3, R^4 =$ 	q
30	5b		1	CH_3CN	23	35	$R^1 = R^2 = H; R^3, R^4 =$ 	r
31	5a	$CH_3COCH{=}CH(CH_2)_2OBz$	0.6	CH_3CN	23	59	$R^1 = R^4 = H; R^2 = (CH_2)_2OBz; R^3 = COCH_3$	s
32	5a	$CH_3COCH{=}CH(CH_2)OSi+$	0.4	CH_3CN	23	78	$R^1 = R^4 = H; R^2 = (CH_2)_2OSi+; R^3 = COCH_3$	t



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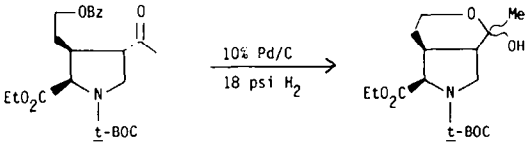
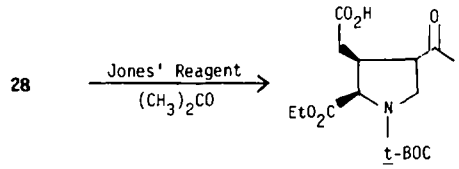
room temperature, giving rise to some fine splitting of signals[35] especially in the ^{13}C-NMR spectra.



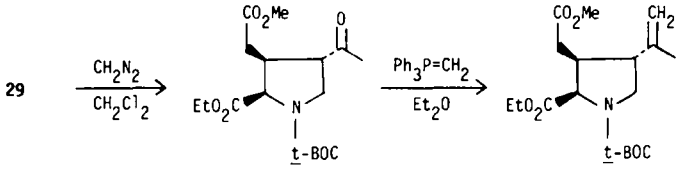
22a 28

Jones' oxidation of hemiketals **28** yielded the carboxylic acid **29** as a white, highly crystalline compound. Both a single crystal X-ray structure and an elemental analysis confirmed this as the correct structure.[36]



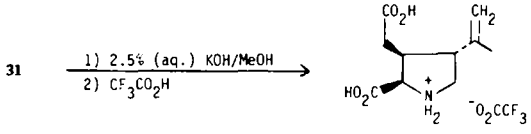
29

Conversion of the free acid into the methyl ester **30** with diazomethane, followed by addition of methylenetriphenylphosphorane, gave the isopropenyl **31**.



30 31

Saponification of both esters and removal of the N-t-butoxycarbonyl group yielded amino diacid **32**, which was isolated as the trifluoroacetate salt.



32

We anticipated that epimerization of the C-2 acid group to the *trans* configuration of **24** might occur during the hydrolysis reaction, but this was not the case. A 300 MHz NMR spectrum showed significant differences between our synthetic material and that of an authentic sample supplied to us by Dr Ohfune. Our initial attempts to epimerize **31** or **32** with either equilibrating bases (DBU, t-butoxide/t-butanol) or strong bases (lithium-2,2,6,6-tetramethyl piperidide, lithium diisopropylaminde) were unsuccessful.

We found that L-proline was almost completely racemized by the action of 0.5 N NaOH aq at a temperature of 175–180° in a sealed tube. This result indicated to us that moderately high temperatures in very polar media were required to form the dianion of proline.

We cautiously subjected **32** to similar conditions and observed that substantial amounts of highly insoluble polymeric material were formed above 155°. A 300 MHz NMR spectrum of the soluble portion of the reaction mixture showed approximately 20% of a material having an identical spectrum to the authentic **24**. Repeating the reaction keeping the temperature slightly below 155° caused only small amounts of polymer to form, and the conversion occurred in 30–50% yield.

In our synthesis, two of the three asymmetric centers are correctly set by the initial dipolar cyclization, making this method superior to the earlier non-stereoselective routes. Only the Oppolzer synthesis offers the advantage of stereospecific molecular construction. Our methodology promises to afford convergent approaches to other pyrrolidine-based natural products. We are presently involved in a synthesis of domoic acid using **16o**.

EXPERIMENTAL

General. Diethyl ether, benzene and THF were distilled from LAH, EtOH from CaH_2, and t-BuOH from NaH. DMF and acetonitrile were dried over 4 Å molecular sieves. All organic extracts were dried over Na_2SO_4. M.ps were determined on a Fisher–Johns m.p. apparatus and are uncorrected. IR spectra were determined on a Beckman Acculab 2 spectrometer. NMR spectra were determined on an Hitachi Perkin–Elmer R-20B 60 MHz or a Varian EM-360 instrument in $CDCl_3$ with absorptions recorded in ppm downfield from internal Me_4Si. High resolution mass spectra were recorded on an AEI MS-902 high resolution mass spectrometer. Low resolution mass spectra were recorded on a Finnigan 4023 mass spectrometer. ^{13}C-NMR spectra were determined on a JEOL FX-90Q Fourier transform spectrometer, with absorptions expressed in ppm relative to the chemical shift of $CDCl_3$. Analyses were performed by Galbraith Laboratories.

General procedure for 1,3-dipolar cycloadditions of thiazolium ylides generated from salts to olefins

In DMF. A soln of the thiazolium salt (2.0 mmol) in DMF (5.0 ml) with the olefinic adduct was prepared. The temp (Table 1) was adjusted and neat Et_3N (2.0 mmol) was slowly added. The resulting orange-colored soln was stirred at this temp for 3 hr, after which time the mixture was diluted with ether (25 ml)

and was washed three times with brine. The organic extract was dried over Na_2SO_4 and removal of the solvents gave a colored residue of the crude addition product. Passage of the residue over a short silica gel column (with EtOAc–hexane, 1 : 10) gave pure adduct as a mixture of isomers at C-8a and C-9a. Only the major isomer is reported in the 60 MHz NMR spectra.

In CH_3CN. A slurry of the thiazolium salt (2.0 mmol) in CH_3CN (3.0 ml) with the olefinic adduct was prepared. The temp (Table 1) was adjusted and neat Et_3N (2.0 mmol) was slowly added. The resulting soln was stirred at this temp for 3 hr, after which time the mixture was diluted with ether (25 ml) and was washed three times with brine. The organic extract was dried over Na_2SO_4. Removal of the solvents gave a residue of the crude addition product. Passage of the residue over a short silica gel column (with EtOAc–hexane, 1 : 10) gave pure adduct as a mixture of isomers at C-8a and C-9a. Only the major isomer is reported in the 60 MHz NMR spectra.

Adduct **16a**. The m.p. was found to be 76–78.5° (from hexane). IR (film) 2980, 1730, 1440, 1365, 1170, 1020 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.32 (t, J = 7 Hz, 6H), 1.60 (bs, 3H), 2.0–3.0 (m, 4H), 3.5–4.6 (m, 5H), 4.45 (bq, J = 7 Hz, 4H), 5.5 (bd, J = 8 Hz, 1H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 13.78 (2C), 22.24, 29.20, 33.62, 46.30, 55.08, 60.67 (2C), 60.80, 65.87, 74.98, 109.83, 170.18, 172.72. High resolution mass spectrum for $C_{15}H_{23}NO_5S$ requires *m/e* 329.12970; found *m/e* 329.13084.

Adduct **16b**. 60 MHz NMR ($CDCl_3$) δ 1.00 (d, J = 6 Hz, 3H), 1.28 (t, J = 7 Hz, 3H), 1.45 (s, 3H), 2.1–2.4 (m, 3H), 2.23 (s, 3H), 3.6–4.3 (m, 5H), 4.25 (bq, J = 7 Hz, 2H), 5.55 (bd, J = 5 Hz, 1H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 14.11, 21.72, 27.05, 30.24, 33.49, 34.47, 34.79, 40.90, 58.14, 59.83, 60.22, 60.54, 61.91, 63.21, 63.66, 64.23, 65.48, 68.61, 71.53, 71.99, 103.72, 107.69, 172.66, 203.61, 205.82. (Found: C, 57.31; H, 7.22. Calc for $C_{15}H_{23}NO_4S$: C, 57.50; H, 7.40%.)

Adduct **16c**. The m.p. was found to be 155–159° (from hexane). IR (film) 2990, 1710, 1580, 1160 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.92 (bd, J = 7 Hz, 3H), 1.34 (bs, 3H), 2.1–2.4 (m, 3H), 2.24 (bs, 6H), 3.2–3.5 (m, 2H), 3.7–4.1 (m, 3H), 5.52 (bd, J = 5 Hz, 1H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 14.37, 22.50, 28.81, 29.72, 33.95, 42.73, 56.71, 61.84, 66.33, 72.25, 74.85, 109.97, 203.09, 210.96. High resolution mass spectrum for $C_{12}H_{18}NO_2S$ (parent minus C_2H_3O) 240.10583; found 240.10536.

Adduct **16e**. 60 MHz NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.55 (s, 3H), 2.0–2.4 (m, 4H), 2.22 (bs, 6H), 3.6–4.5 (m, 10H), 3.70 (bs, 12H), 5.0–5.5 (m, 4H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 22.43, 22.63, 25.23, 25.62, 26.53, 27.51, 32.84, 33.82, 46.69, 48.64, 49.74, 50.98, 51.24, 52.41, 52.74, 56.05, 56.51, 56.64, 66.27, 66.98, 69.26, 69.52, 70.82, 71.86, 73.74, 110.03, 110.23, 169.73, 170.64, 170.77, 171.22, 171.49, 172.01, 208.68, 209.01.

Adduct **16g**. IR (film) 2950, 1735, 1430, 1185, 1025 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.30 (t, J = 7 Hz, 3H), 1.60 (s, 3H), 1.9–2.6 (m, 2H), 3.5–4.4 (m, 6H), 3.70 (s, 3H), 3.75 (s, 3H), 4.20 (q, J = 7 Hz, 2H), 5.28 (d, J = 5 Hz, 1H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 13.85, 22.11, 33.62, 48.58, 49.10, 51.63, 52.41, 55.34, 61.39, 61.91, 65.74, 72.57, 108.21, 169.73, 170.64, 171.87. High resolution mass spectrum for $C_{16}H_{23}NO_7S$ requires *m/e* 373.11953; found *m/e* 373.11858.

Adduct **16l**. 60 MHz NMR ($CDCl_3$) δ 1.40 (bs, 3H), 1.58 (bs, 3H), 1.9–2.4 (m, 4H), 2.40 (bs, 12H), 3.5–4.5 (m, 12H), 5.10 (d, J = 7 Hz, 1H), 5.52 (d, J = 7 Hz, 1H), 7.16 (bs, 10H). (Found: C, 65.87; H, 6.22. Calc for $C_{19}H_{23}NO_3S$: C, 66.06; H, 6.71%.)

Adduct **16s**. IR (film) 2950, 1740, 1720, 1180, 1160 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 1.42 (s, 3H), 2.08 (s, 3H), 2.1–2.3 (m, 5H), 3.1–4.5 (m, 9H), 4.35 (s, 2H), 5.45 (d, J = 5 Hz, 1H), 7.28 (s, 5H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 13.89, 21.84, 22.24, 27.12, 29.85, 30.63, 33.00, 34.08, 37.20, 38.89, 56.51, 57.75, 59.76, 60.28, 60.74, 63.47, 65.35, 66.20, 68.02, 68.67, 68.93, 70.82, 72.57, 74.65, 107.62, 109.64, 127.52, 128.17, 138.19, 171.94, 172.53, 203.22, 203.87. (Found: C, 66.23; H, 7.49. Calc for $C_{20}H_{27}NO_3S$: C, 66.46; H, 7.53%.)

Diethyl 2,4-*pyrrole dicarboxylate* (**17**)

Adduct **16a** (0.44 g, 1.3 mmol) was treated with methane sulfonic acid (0.20 ml, 3.1 mmol) in MeOH (20 ml). A TLC analysis (silica gel, hexane : EtOAc, 1 : 1) revealed only origin material. The soln was poured into a mixture of Et_3N (2.5 ml, 18 mmol) and MeOH (10 ml) and stirred for 4 hr. The soln was evaporated to a residue and then redissolved in dry THF (10 ml). Excess NaH (hexane washed) was added, and the reaction was allowed to stir at room temp protected by a drying tube ($CaSO_4$) for 24 hr. Addition of H_2O (50 ml) followed by extraction with CH_2Cl_2 three times, drying (Na_2SO_4) and evaporation gave a small amount of **17** (0.05 g). Compound **17** had identical R_f on TLC plates (silica gel) and 60 MHz NMR spectrum as diethyl 2,4-pyrrole dicarboxylate prepared by the known procedure. 60 MHz NMR ($CDCl_3$) δ 1.38 (bt, J = 7 Hz, 6H), 4.37 (dq, J = 7 Hz, 4H), 7.37 (dd, J = 1 Hz, 1H), 7.64 (dd, J = 1 Hz, 1H). Low resolution mass spectrum for $C_{10}H_{13}NO_4$ requires *m/e* 211.0; found 211.0, fragments: 196.0, 183.0, 166.0, 140.0, 120.0.

3,5-*Dicarbethoxy*-Δ^2-*pyrroline* (**18**)

A suspension of **16a** (0.33 g, 1.0 mmol) stirred in H_2O (10 ml) containing a catalytic amount of $NaHCO_3$ was prepared. To this suspension a $AgNO_3$ (2.2 ml, 0.5 N (aq)) soln was added dropwise. The mixture became turbid, and after about 1 hr, a yellow residue had settled out, and the soln was extracted four times with CH_2Cl_2. Drying of the organic layer over Na_2SO_4 followed by evaporation gave 0.14 g (0.67 mmol, 67%) of **18** as a very pure yellow isolate which tended to decompose upon standing: 60 MHz NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3H), 1.32 (t, J = 7 Hz, 3H), 3.04 (bs, 1H), 3.17 (bs, 1H), 4.2–4.8 (m, 1H), 4.22 (q, J = 7 Hz, 2H), 4.30 (q, J = 7 Hz, 2H), 5.1 (s, 1H), 7.3–7.4 (m, 1H). The NMR data compared favorably to the lit.[23] Low resolution mass spectrum for $C_{10}H_{15}NO_4$ requires *m/e* 213.0; found *m/e* 213.0, fragments: 140.0, 96.0, 68.0.

Diethyl 2,4-*pyrrolidine dicarboxylate* (**19**)

Enamine **18** (0.40 g, 1.8 mmol) was dissolved in dry EtOH (4 ml) containing a trace amount of bromocresol green (as indicator). 2 N HCl in EtOH was added until the soln turned yellow. Solid $NaCNBH_3$ (0.13 g, 2.1 mmol) was added in one portion, followed by subsequent small additions of 2 N HCl in EtOH when the indicator turned green. After the color no longer changed to green, within 20 min excess solid Na_2CO_3 (~1 g) was added, and the EtOH was removed by evaporation. The residue was taken up in CH_2Cl_2 and washed three times with sat $NaHCO_3$ aq. Drying over Na_2SO_4, followed by evaporation, gave 0.33 g (1.54 mmol, 86%) of **19** as a mixture of diastereomers: IR (film) 3500, 2990, 1730, 1450, 1375, 1185, 1030 cm^{-1}; 60 MHz NMR ($CDCl_3$) (major isomer) δ 1.28 (t, J = 7 Hz, 6H), 2.2–2.5 (m, 2H), 2.75 (bs, 1H), 2.9–3.4 (m, 2H), 3.65–4.1 (m, 2H), 4.22 (q, J = 7 Hz, 4H). High resolution mass spectrum for $C_{10}H_{17}NO_4$ requires *m/e* 215.11576; found *m/e* 215.11526.

Enamine **20**. Adduct **16b** (1.20 g, 3.80 mmol) was dissolved in CH_2Cl_2 : t-BuOH (20 ml : 40 ml) containing CH_3I (0.5 ml, 8.0 mmol) and cooled to 0°. Solid t-butanol : t-butoxide complex (1 : 1) (0.74 g, 4.00 mmol) was added in one portion yielding an orange–yellow heterogeneous soln. The reaction was stirred under N_2 for 3 hr, then warmed to room temp. A TLC analysis (silica gel, hexane–EtOAc, 1 : 1) indicated that no starting material was present.

The solvents were then removed by evaporation. The last traces of t-BuOH were carefully eliminated by azotropic evaporation with benzene. The residue was taken up in MeOH (20 ml) and filtered. The solvent was once again evaporated, then redissolved in CH_2Cl_2 and washed once with sat NaCl aq. The aqueous layer was extracted three times with CH_2Cl_2. All the organic layers were combined and dried over Na_2SO_4. Evaporation gave 1.05 g (3.20 mmol, 84%) of **20** as a set of diastereomers: (major) 60 MHz NMR ($CDCl_3$) δ 1.14 (d, J = 7 Hz, 3H), 1.33 (t, J = 7 Hz, 3H), 1.53 (s, 3H), 2.0–2.5 (m, 2H), 2.22 (s, 3H), 2.25 (s, 3H), 3.12 (t, J = 8 Hz, 2H), 3.4–4.0 (m, 2H), 4.28 (q, J = 7 Hz, 2H), 4.54 (d, J = 10 Hz, 1H), 7.49 (s, 1H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 14.24, 15.35, 25.88, 26.47, 31.54, 33.29, 37.65, 56.97, 60.48, 66.98, 95.33, 117.77, 148.79, 170.44, 190.93.

Low resolution mass spectrum for $C_{16}H_{25}NO_4S$ requires *m/e* 327.0; found 327.1, fragments: 197.1, 154.1, 130.0, 84.0.

Enamine **21**. Adduct **16s** (4.46 g, 10.3 mmol) was eliminated with t-butanol: t-butoxide (1:1) in a similar procedure as that employed for **16b**. Isolation gave 3.33 g (7.4 mmol, 72%) of **21** as a mixture of three diastereomers which were separated by flash chromatography (silica gel: 230–400 mesh): IR (film) 2990, 1745, 1575, 1455, 1380, 1185, 1025 cm^{-1}; (major) 60 MHz NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3H), 1.43 (s, 3H), 1.7–2.5 (m, 4H), 2.16 (s, 3H), 2.18 (s, 3H), 3.00 (t, J = 8 Hz, 2H), 3.3–4.3 (m, 2H), 3.45 (t, J = 7 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 4.45 (s, 2H), 4.45 (d, J = 10 Hz, 1H), 7.23 (s, 5H), 7.37 (s, 1H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 14.11, 25.17, 25.82, 25.95, 29.52, 31.60, 33.23, 39.34, 55.54, 60.54, 67.37, 68.61, 72.38, 95.01, 116.27, 127.20, 127.59, 128.11, 138.84, 149.96, 169.99, 191.32; (1st minor) 60 MHz NMR ($CDCl_3$) δ 1.19 (t, J = 7 Hz, 3H), 1.64 (s, 3H), 1.9–2.6 (m, 4H), 2.15 (s, 3H), 2.19 (s, 3H), 2.8–3.2 (m, 2H), 3.3–4.1 (m, 4H), 4.12 (q, J = 7 Hz, 2H), 4.19 (d, J = 14 Hz, 1H), 4.50 (s, 2H), 7.21 (s, 1H), 7.27 (s, 5H); (2nd minor) 60 MHz NMR ($CDCl_3$) δ 1.22 (t, J = 7 Hz, 3H), 1.66 (s, 3H), 1.9–2.6 (m, 4H), 2.11 (s, 3H), 2.13 (s, 3H), 2.8–3.2 (m, 2H), 3.3–4.1 (m, 4H), 4.09 (q, J = 7 Hz, 2H), 4.15 (d, J = 14 Hz, 1H), 4.45 (s, 2H), 7.09 (s, 1H), 7.23 (s, 5H).

Reduction and cleavage of **16a** *by tri-*n*-butyltin hydride*

Adduct **16a** (0.474 g, 1.44 mmol) was added to a soln of distilled benzene (10 ml) and tri-n-butyltin hydride containing a catalytic amount (10 molar %) of AIBN. The soln was heated at reflux for 1–3 hr. A TLC analysis (silica gel, hexane–EtOAc, 1:1) indicated that there was no starting material present. After the reaction was cooled to room temp, excess 2 N HCl in EtOH (anhydrous, 5 ml) was added, and the mixture was stirred for 3 hr. The solvents were then removed by evaporation, and the yellow residue was taken up into 2 N HCl and washed three times with ether. The aqueous layer was made basic with solid $NaHCO_3$ and then extracted four times with CH_2Cl_2. The CH_2Cl_2 extract was dried over Na_2SO_4 and evaporated giving 0.136 g (0.63 mmol, 45%) of **19** as a viscous yellow oil. The IR and NMR were identical to the compound prepared from **18**.

Reduction and cleavage of **16g** *by tri-*n*-butyltin hydride*

Adduct **16g** (0.252 g, 0.67 mmol) was reduced and cleaved by tri-n-butyltin hydride followed by acidic ethanol in a procedure similar to that employed for **16a**. Isolation gave 0.103 g (0.42 mmol, 63%) of **23** as a yellow oil: IR (film) 3500, 2990, 1730, 1600, 1530, 1435, 1200, 1020 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3H), 3.2–4.3 (m, 5H), 3.65 (s, 3H), 3.70 (s, 3H), 4.20 (q, J = 7 Hz, 2H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 13.92, 49.16, 51.76, 52.28, 52.54, 61.52, 61.73, 61.91, 170.77, 171.16, 172.00.

Reduction and cleavage of **16s** *by tri-*n*-butyltin hydride*

Adduct **16s** (1.8 g, 4.18 mmol) was reduced and cleaved by tri-n-butyltin hydride, followed by acidic EtOH, in a procedure similar to that employed for **16a**. Isolation gave 1.08 g (3.39 mmol, 81%) of **22** as a yellow oil: IR (film) 3440, 2940, 2870, 1730, 1710, 1450, 1365, 1180, 1090 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3H), 1.5–1.8 (m, 2H), 2.06 (s, 3H), 2.7–3.2 (m, 3H), 3.2–3.6 (m, 3H), 3.86 (d, J = 7 Hz, 1H), 4.14 (q, J = 7 Hz, 2H), 4.40 (s, 2H), 7.28 (s, 5H); 90 MHz ^{13}C-NMR ($CDCl_3$) δ 13.85, 29.20, 29.78, 42.20, 49.36, 56.77, 60.28, 63.92, 68.35, 72.44, 127.33 (3C), 127.91 (2C), 137.86, 172.72, 208.16.

Hemiketal **28**. N - t - Butoxycarbonyl - 3α - (2 - benzyloxyethyl) - 4β - acetyl - α - proline - ethyl - ester **22a** (0.45 g, 1.08 mmol) was dissolved in 95% ethanol (3 ml) containing a suspension of 10% Pd/C (0.5 g). A hydrogen pressure of 18 psi was applied on a Parr shaker apparatus. The reaction was shaken for approximately 1 hr and followed to completion by TLC analysis (silica gel, hexane–EtOAc, 2:1). The soln was filtered through celite and the solvent removed leaving 0.26 g (0.80 mmol, 79%) of **28** as a mixture of diastereomers: IR (film) 3500, 2990, 1740, 1700, 1400, 1380, 1190 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.28 (t, J = 7 Hz, 3H), 1.45 (s, 9H), 1.46 (s, 3H), 2.0–2.4 (m, 4H), 3.1–3.8 (m, 4H), 4.1–4.5 (m, 1H), 4.20 (q, J = 7 Hz, 2H); 90 MHz ^{13}C-NMR ($CDCl_3$) (major isomer) δ 14.11, 15.09, 22.83, 28.09, 38.37, 46.30, 47.86, 55.41, 60.48, 61.97, 79.60, 97.74, 153.73, 171.09.

N - t - *Butoxycarbonyl* - 3α - *carboymethyl* - 4β - *acetyl* - α - *proline* - *ethyl* - *ester* (**29**)

Hemiketal **28** (0.129 g, 0.39 mmol) was dissolved in acetone (5 ml). A soln of Jones' reagent (0.5 ml, 8 N dissolved in 7 ml acetone) was added dropwise until a red–brown color persisted for 15 min. Two drops of i-PrOH were added to discharge the color. The soln was diluted with ether (10 ml) and filtered through paper. The solvents were removed by evaporation, the residue was taken up in ether and extracted four times with 1 N Na_2CO_3. The aqueous extract was made acidic with conc HCl, extracted four times with CH_2Cl_2, and the extract dried over Na_2SO_4. Evaporation gave 0.081 g (0.24 mmol, 63%) of **29** as a fine white crystalline solid: m.p. 132–133° (CCl_4); IR (in CH_2Cl_2) 3020, 2990, 1735, 1705, 1400, 1365, 1255, 1195, 1160, 1140 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3H), 1.41 (s, 9H), 2.2–2.6 (m, 3H), 2.19 (s, 3H), 2.9–3.4 (m, 3H), 4.15 (q, J = 7 Hz, 2H), 4.4–4.6 (m, 1H), 7.8 (bs, 1H); 90 MHz ^{13}C-NMR ($CDCl_3$) (major isomer) δ 14.18, 28.29, 34.40, 39.41, 48.12, 52.67, 53.58, 61.32, 62.04, 80.70, 153.47, 171.55 (2C), 206.47. (Found: C, 56.16; H, 7.63. Calc for $C_{16}H_{25}NO_7$: C, 55.97; H, 7.34%.)

N - t - *Butoxycarbonyl* - 3α - *methoxycarbonylmethyl* - 4β - *acetyl* - α - *proline* - *ethyl* - *ester* (**30**)

Acid **29** (0.077 g, 0.22 mmol) was dissolved in CH_2Cl_2 (3 ml) and excess CH_2N_2 (0.5 N in Et_2O) was added dropwise until a yellow color persisted. The solvents and excess reagents were removed by evaporation leaving 0.078 g (0.22 mmol, 100%) of **30** as colorless oil: IR (film) 2980, 1735, 1700, 1390, 1360, 1250, 1190, 1160, 1125 cm^{-1}; 60 MHz NMR ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3H), 1.43 (s, 9H), 2.1–2.5 (m, 3H), 2.19 (s, 3H), 2.8–3.5 (m, 3H), 3.66 (s, 3H), 4.15 (q, J = 7 Hz, 2H), 4.2–4.6 (m, 1H); 90 MHz ^{13}C-NMR ($CDCl_3$) (major isomer) δ 14.18, 28.22, 33.75, 39.41, 48.06, 51.76, 52.54, 61.06, 61.71, 61.91, 80.51, 153.34, 171.29, 171.42, 205.87.

N - t - *Butoxycarbonyl* - 3α - *methoxycarbonylmethyl* - 4β - *isopropenyl* - a - *proline* - *ethyl* - *ester* (**31**)

A soln of **30** (0.030 g, 0.085 mmol) in dry Et_2O (1 ml) was added to a cooled (0°) soln of methylenetriphenylphosphorane (0.053 g, 0.13 mmol triphenylmethylphosphonium iodide and 0.11 mmol of n-BuLi) in Et_2O (4 ml) under N_2. The initial rust-red colored soln turned white and gave a ppt upon addition. The soln was allowed to stir for 2 hr, then the mixture was allowed to rise to ambient temp. Filtration, followed by removal of the solvent, gave a yellow oil, which was flash chromatographed (silica gel: 230–400 mesh, hexane–EtOAc, 10:1). Isolation gave 0.017 g (0.048 mmol, 57%) of **31** as a clear oil: 60 MHz NMR ($CDCl_3$) δ 1.25 (t, J = 7 Hz, 3H), 1.43 (s, 9H), 1.80 (s, 3H), 2.1–2.4 (m, 2H), 2.4–2.9 (m, 2H), 3.0–3.4 (m, 1H), 3.5–3.8 (m, 1H), 3.67 (s, 3H), 4.13 (q, J = 7 Hz, 2H), 4.3–4.6 (m, 1H), 4.84 (bs, 2H); 90 MHz ^{13}C-NMR ($CDCl_3$) (major isomer) δ 14.24, 18.60, 28.35, 33.36, 40.64, 48.38, 49.36, 51.70, 60.93, 61.84, 80.12, 114.65, 141.31, 153.60, 171.55, 172.07.

3α-*Carboxymethyl*-4β-*isopropenyl*-α-*proline* (**32**)

Diester **31** (0.017 g, 0.048 mmol) was dissolved in KOH aq (3 ml, 2.5%) and MeOH (0.5 ml) and brought to reflux (66°) for 2 hr. A TLC analysis (silica gel, hexane–EtOAc, 5:1) indicated none of the material **31** was present in the mixture. The soln was acidified with conc HCl (~3 on pH paper) and evaporated to dryness. Excess trifluoroacetic acid (0.5 ml) was added, and the soln was allowed to stir for 15 min at room temp. The excess CF_3CO_2H was removed by vacuum, yielding a white solid, **32** (along with some KCl): 300 MHz NMR (D_2O, Ref.: TMS cap.) δ 1.71 (s, 3H), 2.42, 2.48 (dd, J = 9.8 Hz, 1H), 2.66, 2.72 (dd, J = 4.9 Hz, 1H), 2.76–2.83 (m, 1H), 2.89–3.00 (m, 1H), 3.25–3.33 (m, 1H), 3.67, 3.71 (dd, J = 8.3 Hz, 1H), 4.68 (d, J = 8.6 Hz, 1H), 4.96 (s, 2H), 5.00 (bs, 4H).

(±)α-*Allokainic acid* (**24**)

The white solid **32** was dissolved in NaOH aq (0.5 N, 1 ml) and freeze–thaw degassed four times. The mixture was sealed in a thick-walled glass tube under N_2. The temp was raised to 130–140° for 5 hr. A very slightly discolored soln along with a small amount of white ppt were obtained. The soln was filtered and evaporated to dryness, yielding a mixture of **32** and **24**. The 300 MHz NMR spectrum of **24** compared exactly to the authentic sample of (±)α-allokainic acid: 300 MHz NMR (D_2O, Ref.: TMS cap.) (disodium salt) δ 1.65 (s, 3H), 2.11–2.30 (m, 1H), 2.4–2.8 (m, 1H), 2.47–2.56 (m, 2H), 2.84–2.87 (m, 2H), 3.03 (d, J = 7.8 Hz, 1H), 4.72 (s, 3H); 300 MHz NMR (D_2O, Ref.: TMS cap.) (trifluoroacetic acid salt) δ 1.69 (s, 3H), 2.72–2.78 (m, 2H), 2.8–3.0 (m, 1H), 3.31 (t, J = 11.3 Hz, 1H), 3.5–3.6 (m, 2H), 4.24 (d, J = 9.2 Hz, 1H), 4.7 (bs, 4H), 5.0 (bs, 2H). The mixture of **32** and **24** has been separated by an ion exchange resin (Dionex DC-6A) with a Durrum model D-400 amino acid analyzer, and their ninhydrin derivatives detected by a 440 nm UV detector. With a flow rate of approximately 31 ml hr^{-1} over a 30 cm column (0.9 cm i.d.), **32** eluted with a retention time of 49.5 (±0.5) min, and **24** eluted with a retention time of 56.4 (±1.2) min with a pH 3.1 buffer (0.67 M sodium citrate). Injection of a mixture of our synthetic **24** and authentic α-allokainic acid showed identical retention times.

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