



# THE SECRET MECHANISM OF ENEDIYNES

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CRAZY  
CHEMIST  
COMICS

**RAIN.**

MAKES ME THINK ABOUT COOL THINGS.

MAKES ME THINK ABOUT BEAUTIFUL THINGS.

MAKES ME THINK ABOUT CHEMISTRY.

BUT THERE ARE DRAWBACKS.

COMPLEX STRUCTURE, NON-SELECTIVITY, UNCONTROLLED REACTIVITY...

SCIENTISTS ARE WORKING 24/7 TO SOLVE THESE ISSUES.

SO AM I.

BUT WHAT IF THERE IS MORE TO ENEDIYNE REACTIVITY?

GOING THROUGH LITERATURE DOESN'T HELP A LOT.

SCIENTISTS PREPARE ENEDIYNE DERIVATIVES AND ACTIVATE THEM THERMICALLY.

THE CONCLUSION: BERGMAN CYCLIZATION OCCURS.

THE THING IS, ALMOST NOBODY ISOLATED THE BERGMAN PRODUCT.

CONCLUSIONS ARE MADE BASED ON A SINGLE PEAK IN DSC.

IN RARE CASES WHEN PRODUCTS ARE ISOLATED, THEY DON'T KNOW WHAT HAPPENS DURING THE ACTIVATION.

TAKING INTO ACCOUNT TEMPERATURES USED FOR THE ACTIVATION, THERE HAS TO BE SOMETHING MORE TO BERGMAN CYCLIZATION MECHANISM. BUT WHAT?

IT'S WORTH INVESTIGATING.

ENEDIYNE ANTIBIOTICS.

THEY KILL TUMOR CELLS BY UNIQUE MECHANISM.

IT'S CALLED BERGMAN CYCLIZATION.

IT OCCURS UPON ACTIVATION.

DESIGNING A MOLECULE THAT COULD SERVE THE PURPOSE.

I NEED FUNCTIONAL GROUPS THAT ARE PRESENT IN COMPOUNDS DESCRIBED IN THE LITERATURE.

I ALSO NEED BIOCOMPATIBILITY.

AND THE ABILITY TO EASILY CHANGE DERIVATIVE PROPERTIES.

AMINO ACIDS MEET ALL THOSE REQUIREMENTS.

I'LL USE DIFFERENT AMINO ACIDS TO SEE THE ROLE OF SIDE-CHAINS.

YES, IT SHOULD DO THE TRICK.

SYNTHESIS SHOULDN'T BE SO COMPLICATED.

INTRODUCTION OF PROTECTION GROUPS.

FOLLOWED BY N-ALKYLATION.

PROBLEMS WITH SONOGASHIRA COUPLING.

SOLVED IT AFTER FEW ATTEMPTS.

ENDED WITH SATISFACTORY YIELDS.

BUT HOW TO MONITOR THE REACTION COURSE DURING HEATING?

THE REMOVAL OF PROTECTION GROUPS AND I'M DONE.

NOW, THE ACTIVATION.

ACETYLENE CORE

AMINO ACID SKELETON

AMINO ACID SIDE-CHAINS

$\alpha: R_1 = -CH_2 (Ala)$   
 $\beta: R_2 = -CH(CH_3) (Val)$   
 $\gamma: R_3 = -CH_2CH_2CH_2 (Leu)$   
 $\delta: R_4 = -H (Gly)$

$\alpha: R_1 = R_2 = -CH_2 (Ala)$   
 $\beta: R_1 = R_2 = -CH(CH_3) (Val)$   
 $\gamma: R_1 = R_2 = -CH_2CH_2CH_2 (Leu)$   
 $\delta: R_1 = -CH(CH_3) (Val), R_2 = -H (Gly)$   
 $\epsilon: R_1 = -CH(CH_3) (Val), R_2 = -CH_2 (Ala)$

CAN IT BE DONE WITH IR SPECTROSCOPY?

LUCKILY, I KNOW A GLY...

YES, IT CAN. BUT IT'S NOT TRIVIAL. EXTENSIVE MEASUREMENTS, TONS OF SPECTRAL DATA, AND TIME... LOTS AND LOTS OF TIME. MOREOVER, I'LL PROBABLY NEED TO MONITOR SEVERAL MOLECULAR VIBRATIONS.

YOU MEAN LIKE SOME SORT OF DISTINCTIVE SIGNAL?

EXACTLY. FOR EXAMPLE, RIGHT HERE, AT 2226 CM<sup>-1</sup>, ARE ACETYLENES. NO SIGNAL, NO ACETYLENES.

I SEE. AND IF YOU COLLECT SPECTRA AT DIFFERENT TEMPERATURES...

...I'LL BE ABLE TO SEE EVERYTHING THAT HAPPENS WITH YOUR COMPOUND AT DESIGNATED TEMPERATURE.

COOL! CAN YOU DO THAT?

"CAN BIRDS FLY?"

2500 Wavenumber

2225

Absorbance vs Wavenumber (cm<sup>-1</sup>)  
 50 °C  
 150 °C  
 250 °C

Absorbance vs T / °C  
 100  
 150  
 200  
 250

To: Matija.Gredicak@rb.hr  
 From: Boris  
 Subject: FTIR thermoanalysis

You definitely have something. You lost one amino group, one carboxyl group, acetylenes are gone... Now, absence of the acetylenes implicates Bergman cyclization. But the other two groups... Try to determine the final product, and from there work on a mechanism. Good luck.

Boris

IT WAS HARD.

HARD AS HELL.

A TON OF MS SPECTRA.

EVEN MORE NMR SPECTRA.

POWERFUL CALCULATIONS.

TWO THEORIES.

AND FINALLY, ONE ANSWER.

I FEEL EMPTY NOW, THOUGH.

ASIMOV WAS RIGHT.

"WE DERIVE SATISFACTION FROM FIGURING OUT THE PUZZLE."

structure confirmed!

Path B confirmed!

3:48

CCOC(=O)C(R1)C(R2)C(R3)C(R4)C(R5)C(R6)C(R7)C(R8)C(R9)C(R10)C(R11)C(R12)C(R13)C(R14)C(R15)C(R16)C(R17)C(R18)C(R19)C(R20)C(R21)C(R22)C(R23)C(R24)C(R25)C(R26)C(R27)C(R28)C(R29)C(R30)C(R31)C(R32)C(R33)C(R34)C(R35)C(R36)C(R37)C(R38)C(R39)C(R40)C(R41)C(R42)C(R43)C(R44)C(R45)C(R46)C(R47)C(R48)C(R49)C(R50)C(R51)C(R52)C(R53)C(R54)C(R55)C(R56)C(R57)C(R58)C(R59)C(R60)C(R61)C(R62)C(R63)C(R64)C(R65)C(R66)C(R67)C(R68)C(R69)C(R70)C(R71)C(R72)C(R73)C(R74)C(R75)C(R76)C(R77)C(R78)C(R79)C(R80)C(R81)C(R82)C(R83)C(R84)C(R85)C(R86)C(R87)C(R88)C(R89)C(R90)C(R91)C(R92)C(R93)C(R94)C(R95)C(R96)C(R97)C(R98)C(R99)C(R100)C(R101)C(R102)C(R103)C(R104)C(R105)C(R106)C(R107)C(R108)C(R109)C(R110)C(R111)C(R112)C(R113)C(R114)C(R115)C(R116)C(R117)C(R118)C(R119)C(R120)C(R121)C(R122)C(R123)C(R124)C(R125)C(R126)C(R127)C(R128)C(R129)C(R130)C(R131)C(R132)C(R133)C(R134)C(R135)C(R136)C(R137)C(R138)C(R139)C(R140)C(R141)C(R142)C(R143)C(R144)C(R145)C(R146)C(R147)C(R148)C(R149)C(R150)C(R151)C(R152)C(R153)C(R154)C(R155)C(R156)C(R157)C(R158)C(R159)C(R160)C(R161)C(R162)C(R163)C(R164)C(R165)C(R166)C(R167)C(R168)C(R169)C(R170)C(R171)C(R172)C(R173)C(R174)C(R175)C(R176)C(R177)C(R178)C(R179)C(R180)C(R181)C(R182)C(R183)C(R184)C(R185)C(R186)C(R187)C(R188)C(R189)C(R190)C(R191)C(R192)C(R193)C(R194)C(R195)C(R196)C(R197)C(R198)C(R199)C(R200)C(R201)C(R202)C(R203)C(R204)C(R205)C(R206)C(R207)C(R208)C(R209)C(R210)C(R211)C(R212)C(R213)C(R214)C(R215)C(R216)C(R217)C(R218)C(R219)C(R220)C(R221)C(R222)C(R223)C(R224)C(R225)C(R226)C(R227)C(R228)C(R229)C(R230)C(R231)C(R232)C(R233)C(R234)C(R235)C(R236)C(R237)C(R238)C(R239)C(R240)C(R241)C(R242)C(R243)C(R244)C(R245)C(R246)C(R247)C(R248)C(R249)C(R250)C(R251)C(R252)C(R253)C(R254)C(R255)C(R256)C(R257)C(R258)C(R259)C(R260)C(R261)C(R262)C(R263)C(R264)C(R265)C(R266)C(R267)C(R268)C(R269)C(R270)C(R271)C(R272)C(R273)C(R274)C(R275)C(R276)C(R277)C(R278)C(R279)C(R280)C(R281)C(R282)C(R283)C(R284)C(R285)C(R286)C(R287)C(R288)C(R289)C(R290)C(R291)C(R292)C(R293)C(R294)C(R295)C(R296)C(R297)C(R298)C(R299)C(R300)C(R301)C(R302)C(R303)C(R304)C(R305)C(R306)C(R307)C(R308)C(R309)C(R310)C(R311)C(R312)C(R313)C(R314)C(R315)C(R316)C(R317)C(R318)C(R319)C(R320)C(R321)C(R322)C(R323)C(R324)C(R325)C(R326)C(R327)C(R328)C(R329)C(R330)C(R331)C(R332)C(R333)C(R334)C(R335)C(R336)C(R337)C(R338)C(R339)C(R340)C(R341)C(R342)C(R343)C(R344)C(R345)C(R346)C(R347)C(R348)C(R349)C(R350)C(R351)C(R352)C(R353)C(R354)C(R355)C(R356)C(R357)C(R358)C(R359)C(R360)C(R361)C(R362)C(R363)C(R364)C(R365)C(R366)C(R367)C(R368)C(R369)C(R370)C(R371)C(R372)C(R373)C(R374)C(R375)C(R376)C(R377)C(R378)C(R379)C(R380)C(R381)C(R382)C(R383)C(R384)C(R385)C(R386)C(R387)C(R388)C(R389)C(R390)C(R391)C(R392)C(R393)C(R394)C(R395)C(R396)C(R397)C(R398)C(R399)C(R400)C(R401)C(R402)C(R403)C(R404)C(R405)C(R406)C(R407)C(R408)C(R409)C(R410)C(R411)C(R412)C(R413)C(R414)C(R415)C(R416)C(R417)C(R418)C(R419)C(R420)C(R421)C(R422)C(R423)C(R424)C(R425)C(R426)C(R427)C(R428)C(R429)C(R430)C(R431)C(R432)C(R433)C(R434)C(R435)C(R436)C(R437)C(R438)C(R439)C(R440)C(R441)C(R442)C(R443)C(R444)C(R445)C(R446)C(R447)C(R448)C(R449)C(R450)C(R451)C(R452)C(R453)C(R454)C(R455)C(R456)C(R457)C(R458)C(R459)C(R460)C(R461)C(R462)C(R463)C(R464)C(R465)C(R466)C(R467)C(R468)C(R469)C(R470)C(R471)C(R472)C(R473)C(R474)C(R475)C(R476)C(R477)C(R478)C(R479)C(R480)C(R481)C(R482)C(R483)C(R484)C(R485)C(R486)C(R487)C(R488)C(R489)C(R490)C(R491)C(R492)C(R493)C(R494)C(R495)C(R496)C(R497)C(R498)C(R499)C(R500)C(R501)C(R502)C(R503)C(R504)C(R505)C(R506)C(R507)C(R508)C(R509)C(R510)C(R511)C(R512)C(R513)C(R514)C(R515)C(R516)C(R517)C(R518)C(R519)C(R520)C(R521)C(R522)C(R523)C(R524)C(R525)C(R526)C(R527)C(R528)C(R529)C(R530)C(R531)C(R532)C(R533)C(R534)C(R535)C(R536)C(R537)C(R538)C(R539)C(R540)C(R541)C(R542)C(R543)C(R544)C(R545)C(R546)C(R547)C(R548)C(R549)C(R550)C(R551)C(R552)C(R553)C(R554)C(R555)C(R556)C(R557)C(R558)C(R559)C(R560)C(R561)C(R562)C(R563)C(R564)C(R565)C(R566)C(R567)C(R568)C(R569)C(R570)C(R571)C(R572)C(R573)C(R574)C(R575)C(R576)C(R577)C(R578)C(R579)C(R580)C(R581)C(R582)C(R583)C(R584)C(R585)C(R586)C(R587)C(R588)C(R589)C(R590)C(R591)C(R592)C(R593)C(R594)C(R595)C(R596)C(R597)C(R598)C(R599)C(R600)C(R601)C(R602)C(R603)C(R604)C(R605)C(R606)C(R607)C(R608)C(R609)C(R610)C(R611)C(R612)C(R613)C(R614)C(R615)C(R616)C(R617)C(R618)C(R619)C(R620)C(R621)C(R622)C(R623)C(R624)C(R625)C(R626)C(R627)C(R628)C(R629)C(R630)C(R631)C(R632)C(R633)C(R634)C(R635)C(R636)C(R637)C(R638)C(R639)C(R640)C(R641)C(R642)C(R643)C(R644)C(R645)C(R646)C(R647)C(R648)C(R649)C(R650)C(R651)C(R652)C(R653)C(R654)C(R655)C(R656)C(R657)C(R658)C(R659)C(R660)C(R661)C(R662)C(R663)C(R664)C(R665)C(R666)C(R667)C(R668)C(R669)C(R670)C(R671)C(R672)C(R673)C(R674)C(R675)C(R676)C(R677)C(R678)C(R679)C(R680)C(R681)C(R682)C(R683)C(R684)C(R685)C(R686)C(R687)C(R688)C(R689)C(R690)C(R691)C(R692)C(R693)C(R694)C(R695)C(R696)C(R697)C(R698)C(R699)C(R700)C(R701)C(R702)C(R703)C(R704)C(R705)C(R706)C(R707)C(R708)C(R709)C(R710)C(R711)C(R712)C(R713)C(R714)C(R715)C(R716)C(R717)C(R718)C(R719)C(R720)C(R721)C(R722)C(R723)C(R724)C(R725)C(R726)C(R727)C(R728)C(R7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